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THE UNIVERSITY OF ALBERTA

DETERMINANTS OF EXCESSIVE RUNNING IN ACTIVITY-ANOREXIA

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND
RESEARCH IN PARTIAL FULFULLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PSYCHOLOGY

EDMONTON, ALBERTA
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Quotation

I never attacked a problem by constructing a Hypothesis. I never deduced Theorems or submitted them to Experimental Check. So far as I can see, I had no preconceived Model of behavior--certainly not a physiological or mentalistic one, and, I believe, not a conceptual one ... Of course, I was working on a basic Assumption--that there was order in behavior if I could only discover it--but such an assumption is not to be confused with the hypotheses of deductive theory. It is also true that I exercised a certain Selection of Facts but not because of relevance to theory but because one fact was more orderly than another. If I engaged in Experimental Design at all, it was simply to complete or extend some evidence of order already observed.

(Skinner, 1956)

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Determinants of Excessive Running in Activity-Anorexia submitted by Douglas Pieter Boer in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

W J Epling

(Supervisor)

H. David Pierce

Carl D Cheney

Date: May 19, 1989

Abstract

The present experiments were designed to identify those factors that control wheel running by rats in the activity-anorexia paradigm described by Epling and Pierce (1988). Briefly, the first and second experiments showed that wheel running increases to excessive levels as body weight declines. The second and third experiments demonstrated that once established, high-rate wheel running is a function of food allocation. Thus, the wheel running observed in activity-anorexia is controlled by two processes. Running initially increases as body weight declines, but following this increase it becomes sensitive to changes in food allocation. Finally, the fourth experiment suggested that high-rate running produces endogenous opioids which maintain activity at excessive levels.

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I. INTRODUCTION

The biobehavioral perspective of "activity-anorexia" proposed by Epling and Pierce (1988) suggests that food deprivation and meal schedule interrelate with physical activity in the production of certain instances of self-starvation. From this perspective, physical activity reduces the value of food reinforcement and this results in decreased food intake. Lower food intake concomitant with a decline in body weight, increases the motivational value of exercise, further reducing the reinforcing value of food. Thus, Epling and Pierce (1988) conclude that food allocation and body weight interact in the generation of excessive activity in activity-anorexia. In most studies the effect of body weight loss and food allocation upon physical activity cannot be isolated (as these two variables are confounded) and the role of these two factors has not been systematically investigated.

Epling and Pierce (1988) also propose that the relationship between exercise and eating is mediated by the endogenous opioid system. Research evidence supports the endogenous opioid mediation of the effects of activity on eating (e.g., Davis, Lamb, Lowy, Yim and Malven, 1985), but the possibility of endogenous opioid mediation of the effects of food deprivation upon activity has not been determined. The present experiments investigate these relationships.

Certain species of animals substantially increase activity as measured by wheel running when they are food-deprived (e.g., Campbell and Sheffield, 1953; Cornish and Mrosovsky, 1965; Finger, 1951, 1965; Hall, 1956; Hall and Hanford, 1954; Hall, Smith, Schnitzer and Hanford, 1953; Treichler and Hall, 1962; Zielinski, 1986). Several authors suggest that this increase in activity is exclusively determined by body weight loss (e.g., Bolles, 1967; Collier, 1969). The majority of these studies have employed single daily meals of two hours or less duration (e.g., Routtenberg and Kuznesof, 1967). However, data reported by Kanarek and Collier (1983) showed that deviations in the standard single meal procedure produced marked changes in activity levels. This suggests that the excessive wheel running observed in activity-anorexia may be dependent on food allocation (Epling and Pierce, 1988; Epling, Pierce and Stefan, 1983). Alternatively, food allocation may affect amount eaten which determines weight loss and this in turn determines wheel turns.

As previously stated, the increase in wheel running activity observed with food deprivation has been attributed to a decrease in body weight (e.g., Bolles, 1967; Collier, 1969; Duda and Bolles, 1963; Moskowitz, 1959; Treichler and Hall, 1962). For example, Collier (1969) reported a study which compared wheel running in two groups of rats, one water deprived and the other food deprived. His results indicate that wheel turning is a linear log log function of percentage body weight loss. In another study, Duda and Bolles (1963) exposed 7 groups of rats to different food deprivation conditions and determined that the main effect of the deprivation conditions was differential weight loss. These authors found that the number of wheel turns made was related to body weight loss independent of number of hours of food deprivation. Therefore, Collier (1969) and Duda and Bolles (1963) conclude that running wheel activity is a function of percentage body weight loss for food deprived animals.

In studies examining body weight loss as a measure of motivation, weight loss and food deprivation are confounded. For example, Duda and Bolles (1963) results reveal that rats deprived of food for 96-hr made significantly more wheel turns than rats deprived of food for only 24-hr. However, these results do not isolate body weight loss as the cause of the activity level difference since the food deprivation schedules are disparate. Similarly, studies examining the effect of food deprivation on running wheel activity confound weight loss and food deprivation. For example, Finger (1951) using rats investigated the effects of two levels of food deprivation (24-hr and 72-hr) upon activity. He found that amount of running wheel activity increased markedly with the extent of deprivation. Again, these results do not isolate food deprivation schedule as the cause of the activity level difference since the schedules produced differential weight loss. In summary, studies examining the effects of body weight loss and meal schedule upon wheel running have not resolved the differential effects of these two factors as they co-vary.

Food restriction and running-wheel availability have been shown to be sufficient conditions for producing excessive locomotor activity in rats (e.g., Routtenberg and Kuznesof, 1967). Epling and Pierce (1984) report that rats exposed to a free wheel and food restriction, initially increased food intake and made a moderate amount of wheel turns. After a few days, as activity increased food intake levelled off, and as activity subsequently peaked food intake markedly declined. During this procedure, body weight decreased as a function of food intake, which was a function of rate of change in daily activity. Epling and Pierce

(1984) conclude that "body weight decline was due to the indirect effects of activity on food intake and the direct effects of rate of wheel running on energy expenditure (p. 37)". Thus, the initial activity observed during activity-anorexia may begin as a function of percentage body weight loss (e.g., Collier, 1969) which is a function of food intake (Epling and Pierce, 1984).

An increase in activity by food restricted animals prior to the scheduled time of feeding termed "anticipatory activity" is well documented in rodents (e.g., Boulous, Rosenwasser and Terman, 1980; Boulous and Terman, 1980; Coleman, Harper, Clarke and Armstrong, 1982; Honma, von Goetz and Aschoff, 1983; Prins, de Jong-Nagelsmit, Keijser and Strubbe, 1986) and certain small carnivores (e.g., Zielinski, 1986). For example, Richter (1922) found that rats on a restricted feeding schedule of 25-min per day increased locomotor activity and that a significant portion of this increase was coupled to the time of feeding. Other research determined that rats placed on a 1-hr/day feeding schedule increased running wheel activity as a function of the number of days of restricted feeding, while control animals on ad libitum food exhibited comparatively constant activity levels (Hall and Hanford, 1954). Data collected by Kanarek and Collier (1983) showed that the imposition of either one 60-min, two 30-min, or four 15-min restricted feeding schedules affected wheel running activity. As meal frequency increased, the level of wheel running decreased. Interestingly, the activity level of the four 15-min meals subjects did not differ from ad libitum controls. Unfortunately, the meal schedule also affected amount eaten and body weight. Despite this confound in the Kanarek and

Collier (1983) study these data suggest that activity level and pattern of activity are related to food allocation.

Epling and Pierce (1988) propose that body weight loss and food allocation interact in the generation of excessive running in activity-anorexia. These authors and others (e.g., Collier, 1969) note that food deprivation resulting in percentage body weight loss reliably produces an increase in locomotor activity. The foraging literature states that an increase in locomotor activity when food supplies within a patch are diminished has survival value (e.g., Krebs, Houston and Charnov, 1981). That is, if an animal is to maximize its net energy gain from foraging in a particular food patch, it should leave the patch when its expected net gain from staying in the present patch decreases to the level of the expected net gain from traveling to and searching in the next food patch (Charnov, 1976). However, Epling and Pierce (1988) suggest that, "during periods of food scarcity, travel should not stop when food is infrequently contacted, since stopping to eat may be negatively balanced against getting to a richer food patch. Increasing contact with food would indicate a replenished supply, and travel should reduce or stop at this time (p. 480)". In addition, Richter (1927) notes that food consumption by rats occurs in meals and therefore changes in total food intake can only result from alterations in meal size or frequency, or both (Johnson, Ackroff, Peters and Collier, 1986). An increase in meal frequency (e.g., dividing a 1-hr feeding period into four 15-min periods) has been shown to reduce wheel running activity (Kanarek and Collier, 1983). Therefore, changes in food density should correspond in an inverse fashion to changes in the amount of wheel running by food restricted rats (cf., Epling, Pierce, Russell, Amy and Boer, 1986).

The excessive running seen in activity-anorexia may begin as a function of percentage body weight loss (e.g., Collier, 1969). However, once established, high activity levels may be sensitive to changes in food allocation (e.g., meal size). Therefore, the control of activity during activity-anorexia may be of a two-factor nature. In other words, loss of weight and/or change in meal pattern may start an animal running but, once it is excessively active, amount of food rather than body weight may control activity.

Pierce, Epling and Boer (1986) report behavioral data which shows that the reinforcing efficacy of wheel running increases with increasing food deprivation. Epling and Pierce (1988) suggest that a physiological mechanism links the motivational value of running and eating. In particular, Epling and Pierce (1988) propose that the endogenous opioid system mediates between locomotor activity and food intake in activity-anorexia once high activity levels are established.

Other studies have shown that endogenous opioids may mediate changes in eating following exercise (e.g., Davis, Lamb, Lowy, Yim and Malven, 1985). In general, opiate antagonists (e.g., naloxone) decrease food or water intake if the endogenous opioid system has been activated by food or water deprivation (e.g., Brands, Thornhill, Hirst and Gowdey, 1979; Brown and Holtzman, 1979; McLaughlin and Baile, 1984a, 1984b; Reid, 1985). However, activation of the endogenous opioid system by physical activity may have differential effects upon eating. For example, Davis et al. (1985) found that rats which were forced to swim and which were injected with 2-deoxy-D-glucose (an endogenous opioid stimulus which increases food consumption) showed depressed post-exercise feeding. Additional research has shown that opiate antagonists cause a reversal in morphine (an opiate agonist) elicited behavior (e.g., Schnur and Hang, 1987). In general, morphine produces increments in food intake (Reid, 1985). However, Sanger and McCarthy (1980) found that morphine decreased food and water intake in 24-hr food deprived rats. Overall, these studies suggest that excessive activity activates endogenous opioids which reduce eating when animals are food deprived.

The effects of food deprivation on locomotor activity may also be mediated by the endogenous opioid system. However, Epling and Pierce (1988) note that no mediating mechanism has been identified to date. Many studies have shown that exercise increases endogenous opioid levels in animals (e.g., Amir, 1982; Walker, Berntson, Paulucci and Champney, 1981) and humans (e.g., Appenzeller, Standefer, Appenzeller and Atkinson, 1980). In addition, endogenous opioids are activated by food deprivation (e.g., Brands, et al. 1979; Brown and Holtzman, 1979; Reid, 1985) and food deprivation increases activity (e.g., Cornish and Mrosovsky, 1965). Taken together, these studies suggest that endogenous opioids may modulate the excessive activity observed in activity-anorexia.

In summary, a two-factor theory of the excessive activity observed in activity-anorexia is investigated. The initial increase in activity may be due to percentage body weight loss and/or meal schedule which affects weight loss. However, once activity is excessive it is sensitive to changes in food allocation. Experiments One and Two indicate that activity varies as a function of percentage body weight loss. The effect of a single scheduled meal in Experiment Two interacted with body weight loss to significantly affect wheel running. Experiment Three showed that, once established, high rate wheel running is sensitive to changes in food allocation. Finally, Experiment Four offers evidence that the endogenous opioid system mediates the relationship between food allocation and activity once wheel running occurs at high rate.

II. EXPERIMENT ONE

A. Introduction

Experiment One examines the relation between the induction of excessive activity observed in activity-anorexia and body weight loss. Body weight loss induced by prolonged moderate food restriction has been shown to induce voluntary prolonged running by rats (Russell, Epling, Pierce, Amy and Boer, 1987). In this study, rats were allowed running-wheel access for 23h per day and a regularly scheduled daily meal of 15g until the number of wheel turns reached 8000 turns per day. The food amount of 15g was determined to be moderate food restriction of 77% normal daily food intake (19.5g/day for sedentary ad libitum rats). An increase in the daily number of wheel turns (the dependent variable) while food allocation (the independent variable) remains constant, would indicate that percentage body weight loss is required for the initial development of excessive running observed in activity-anorexia.

B. Method

1. Subjects

10 male JCR:LA/N-corpulent (lean) six week old rats were obtained from the Health Sciences Laboratory Animal Centre, Clinical Sciences Building, University of Alberta, Edmonton, AB, Canada. The JCR:LA/N-cp rat was developed by Russell and Amy (1986a, 1986b) as a model for the study of atherosclerotic disease. Russell and Amy (1986a, 1986b) have shown that the corpulent males of the JCR:LA/N-cp strain develop atherosclerotic and myocardial lesions. If homozygous for the

cp gene, these rats also display hyperphagia, a VLDL (very low density lipoprotein) hyperlipidemia, and insulin resistance. Russell and Amy (1986a) note that body weight of cp homozygotes reaches 950g compared to 400g for lean heterozygotes. In addition, Ahuja, Manickavel, Amy and Russell (1987) found that rats which are homozygous normal (+/+) or heterozygous (cp/+) are phenotypically identical, lean, and physiologically normal. Homozygous normal (lean) JCR:LA/N-cp rats were used in the present studies. Prior to the experimental procedures the animals were individually housed and maintained on ad libitum food and water.

2. Apparatus

Rats were housed in standard 1.10m circumference Wahmann activity wheels with attached wire side cages and wheel revolution counters (Wahmann Manufacturing, Timonium, MD). Running wheels were placed in individual cubicles, thus not allowing experimental subjects visual contact. Control rats were individually housed in running wheel side cages. All rats were fed a pelleted chow composed of grains and 4.5% fat (Wayne Lab Blox, Allied Mills, Chicago, IL). Water was available on an ad libitum basis throughout the experimental procedure.

3. Procedure

In the room where the rats were housed room lighting was provided on a 12/12 hours on/off basis with lights on at 0600h, and a temperature of 20 ± 2 degrees Celsius was maintained. The animals were brought into the laboratory and randomly assigned to locked running wheels, and body weight, food-intake and water-intake were recorded. All animals were exposed to the experiment at 45 days of age.

At the beginning of the experimental phase, rats were exposed to food restriction of 15g/day. This amount represented 77% of the average amount of food consumed during the ad libitum baseline. Experimental rats were not locked out of running wheels except for daily weighing. The 5 control rats were yoked to experimental subjects and fed the same amount of food at the same time each day as its yoked partner. Rats were maintained on 15g/day until reaching a high rate activity criterion of 8000 revolutions/day. Once a subject attained this criterion it was given 18g/day which decreased high rate activity and reduced the possibility of starvation. An increase in food amount has been shown to decrease high rate activity (Epling, Pierce, Russell, Amy and Boer, 1986).

The dependent variables in this experiment were number of daily wheel revolutions and body weight. Collier (1969) and Duda and Bolles (1963) conclude that the increase in wheel running activity observed with food deprivation is due primarily to a concomitant decrease in body weight. However, these studies confound body weight loss and meal schedule because experimental subjects were food deprived for different periods of time. In the present study, all rats were exposed to the same food deprivation schedule. An increase in the daily number of wheel turns over the length of the experiment while food allocation remains constant would indicate that body weight loss is required for the initial development of the excessive activity observed in activity-anorexia.

C. Results

The purpose of this study was to determine whether the development of excessive wheel running observed in activity-anorexia requires body weight loss. An increase in the daily number of wheel turns while food allocation remains constant would support this claim.

Because the results for all subjects were similar, two subjects were chosen at random and graphed individually (Figures 1.1a and 1.1b) in addition to a graph of the averaged data (Figure 1.2) which is also presented in Table 1.1. An examination of this data shows that wheel running increases slowly as body weight progressively decreases to day 8. At day 9 there is a marked increase in running level (from an average of 5754.6 turns to 7973.8 turns). There is not a corresponding marked decrease in average body weight. The average body weight of the rats on day 9 was 155.5g, which represents 81.7% of average initial body weight. The range of percentage body weight on day 9 was 69.7 to 90.4. Day 9 running level and body weight as a percentage of initial weight for all rats is given in Table 1.2. Pair-fed sedentary control data is shown in Table 1.3. The marginal decrease in average daily weight is due to the results of one rat which lost weight over the 9 days of the experiment. All other controls lost weight on days 1 and 2, but regained and surpassed their initial body weight by day 9.

The average wheel turns and body weight data are represented in Figure 1.3 as log number of wheel turns plotted as a function of log percentage body weight loss (from ad libitum control weight - see Appendix Table 1 and Appendix Figures 1 and 2). This graph (Figure 1.3) shows that number of wheel turns is a linear log log function of percentage body weight loss calculated from ad libitum control weight as suggested by Collier (1969). Figure 1.4 shows that the average number of wheel turns is also a linear function of the untransformed average body weight data. Collier's (1969) linear log log function results in an inflated R^2=0.980 compared to the R^2=0.868 of the untransformed data. Thus, Collier's log log analysis implies that 98% of the variance in wheel turns is explained by percentage body weight loss, while the untransformed data shows that 87% of the variance in wheel turns is explained by experimental day body weight. Since food allocation remained constant over the length of the experiment, differences in running level over the duration of the experiment are attributed to percentage body weight loss. In summary, these data show that body weight loss is required for the initial development of excessive activity observed in activity-anorexia.

D. Discussion

In this experiment body weight loss was induced by moderate food restriction of 15g/day. Rats that had the opportunity to run in a wheel and were food restricted progressively lost weight and increased wheel running to an average of 7973.8 turns/day by day 9. The mean body weight of these rats on day 9 was 81.7% of their initial body weight. Interestingly, high rate running does not occur until rats approach 80% of their initial body weight. Thus, food deprivation alone does not result in immediate high rate wheel running. That is, the rats in this study were not sensitive to the change in food allocation (from free food to 15g/day) as shown by low rates of wheel running in the initial 3 to 5 days of food deprivation. Also, moderate food restriction alone is not sufficient to produce percentage weight loss as shown by the pair-fed sedentary controls which maintained body weight (see Table 1.3). However, such food restriction does decrease the rate of weight increase as compared to ad libitum fed sedentary rats (see Appendix Table 1).

In summary, these results show that rats housed in free activity wheels and exposed to moderate food restriction, lose a percentage of body weight which is required for the initial development of excessive running observed in activity-anorexia.

These data support Bolles (1967) and Collier (1969) in that food deprivation resulting in body weight loss reliably produces an increase in locomotor activity. In addition, the number of wheel turns made is a linear function of experimental body weight and a log log function of body weight loss calculated from ad libitum control weight (see Figures 1.4 and 1.3) as determined by Collier (1969). Thus, it appears that Collier's (1969) conclusion that "an important portion of the variance observed in food-...motivated...spontaneous activity can be accounted for by weight loss (p. 605)" is correct. However, as shown previously, his analysis results in a spuriously high correlation which does not accurately reflect the actual correlation that exists between the wheel turns and body weight data during food deprivation.

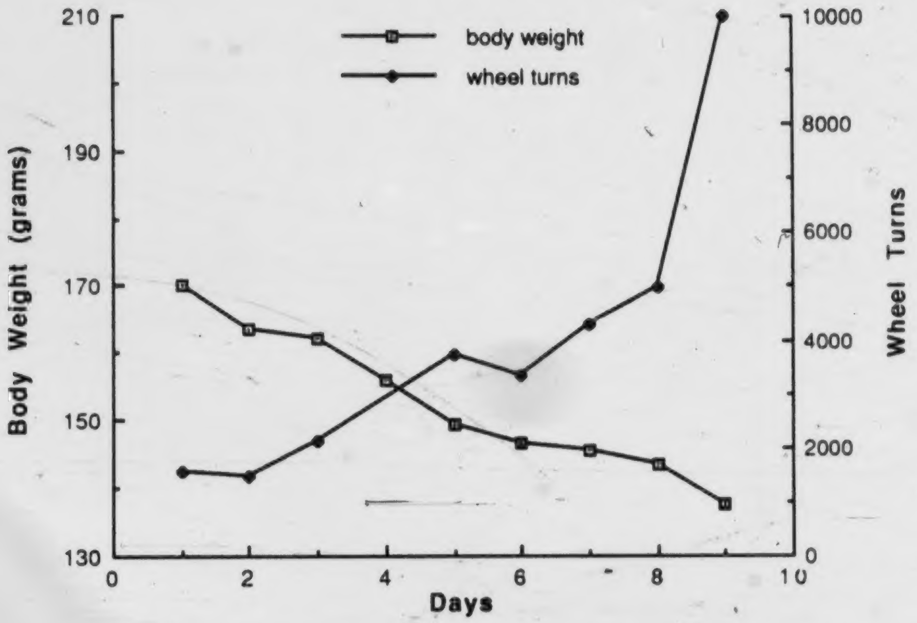


Figure 1.1a: daily number of wheel turns and body weight for rat 8469 for total time of experiment.

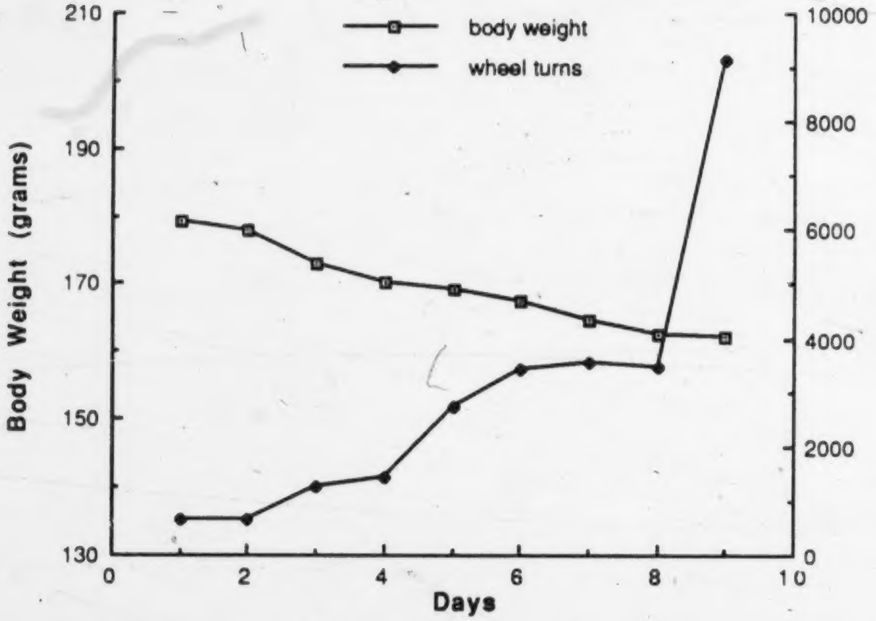


Figure 1.1b: daily number of wheel turns and body weight for rat 8452 for total time of experiment.

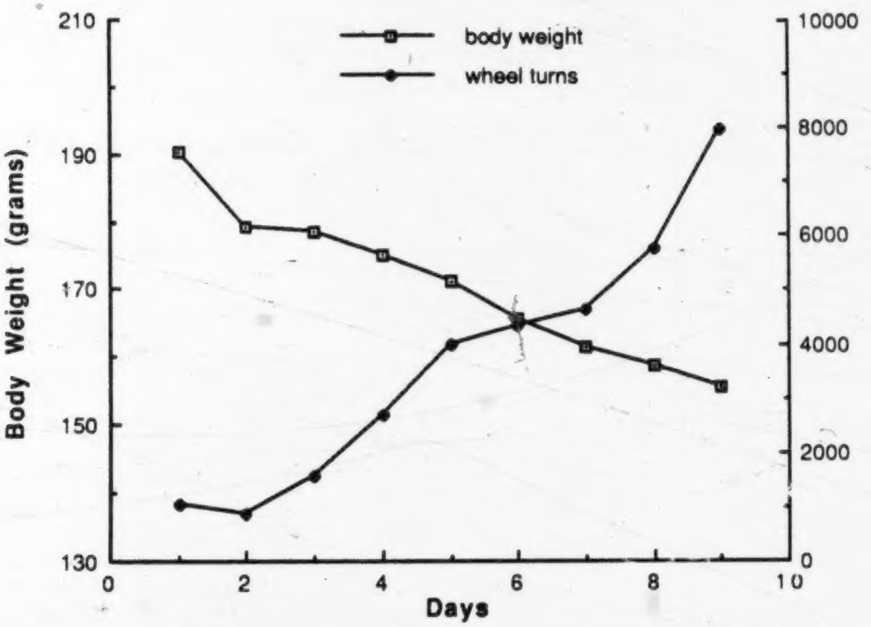


Figure 1.2: average daily number of wheel turns and body weight for all rats (N=5) for total time of experiment.

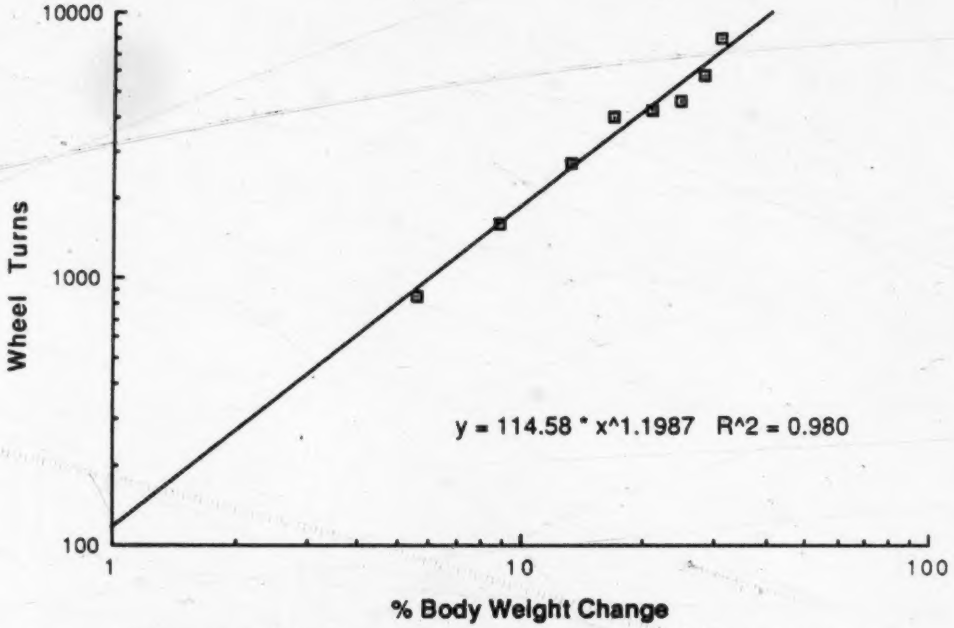


Figure 1.3: log number of wheel turns as a function of log percentage body weight loss for all rats (N=5).

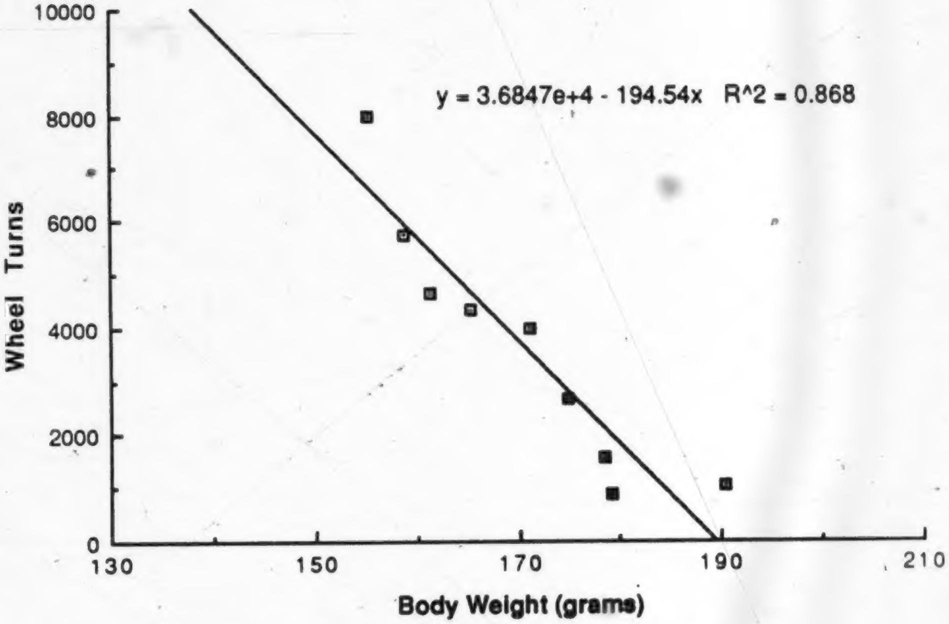


Figure 1.4: average number of wheel turns as a function of average body weight for all rats (N=5).

Table 1.1

Average and range of daily body weight and wheel turns for all rats (N=5) for experiment one.

Days	Body Weight(gms)		Wheel Turns	
	Average	Range	Average	Range
1	190.3	170.3-206.2	1043.8	14-2197
2	179.3	163.7-196.0	858.0	9-1792
3	178.5	162.1-195.4	1588.6	813-2597
4	174.9	155.9-192.1	2689.0	1446-5406
5	171.3	149.3-188.9	3996.2	2739-6906
6	165.5	146.7-181.4	4320.4	3010-7728
7	161.5	145.7-176.0	4646.8	2726-8006
8	158.9	143.5-174.4	5754.6	3457-9539
9	155.5	137.6-171.7	7973.8	5989-10017

Table 1.2

Range of body weight and day 9 percentage body weight and no. of wheel turns for all rats (N=5) for experiment one.

Rat no.	Body Weight (gms)		Wheel Turns (day 9)
	Range (day 1-9)	% on day 9	
8452	179.3-162.1	90.4	9134
8469	170.0-137.6	80.9	10017
8453	200.6-139.8	69.7	5989
8445	195.0-166.3	85.3	6939
8446	206.2-171.7	83.3	7790

Table 1.3

Average and range of daily body weight for all 15g/day sedentary control rats (N=5) for experiment one.

Days	Body Weight(gms)	
	Average	Range
1	190.0	182.4-200.0
2	182.9	173.0-193.7
3	182.2	170.6-194.8
4	182.0	166.4-194.6
5	183.5	169.2-196.2
6	184.0	165.2-198.1
7	185.3	164.9-199.4
8	185.0	162.7-199.6
9	185.5	162.0-202.5

III. EXPERIMENT TWO

A. Introduction

Experiment Two examines the effects of food allocation and percentage weight loss by examining the effects of a single 90 minute meal/day versus zero grams of food/day on the development of excessive activity. If excessive running is controlled by relative weight loss alone (e.g., Bolles, 1967; Collier, 1969; Kanarek and Collier, 1983), then animals receiving no food should lose weight and increase running more rapidly than animals receiving a single meal per day. However, Hamilton (1969) showed that rats receiving ad libitum edible nonnutritive bulk during a 5-day starvation period were much less active than fasted rats not receiving the bulk during this period. An examination of Hamilton's (1969) results shows that the rats which consumed an average of 16g/day of bulk did not differ in daily body weight from the fasted rats not receiving the bulk. Thus, the excessive running observed in activity-anorexia may be dependent on body weight loss interacting with food allocation.

If the presentation of a single meal is important in the production of excessive wheel running, then the rats receiving a fixed daily meal may increase activity more rapidly than the rats receiving no food at all. Thus, the relative importance of weight loss and a fixed daily meal in the production of excessive wheel running may be determined by this study. Interestingly, if the single meal animals lose weight more quickly than the no-food animals, the interaction between meal schedule and body weight may be of central importance in the production of excessive activity in activity-anorexia.

B. Method

1. Subjects

Three groups of male JCR:LA/N-corpulent (lean) rats were obtained from the Health Sciences Laboratory Animal Centre, Clinical Sciences Building, University of Alberta, Edmonton, AB, Canada. Group 1 consisted of 8 six week old rats (mean initial weight of156.5g, S.D.=8.6). Group 2 consisted of 8 eight week old rats (mean initial weight of 240.9, S.D.=12.1). Group 3 consisted of 7 seventeen week old rats (mean initial weight of 352.8g, S.D.=16.9). Prior to the experimental procedures the animals were individually housed and maintained on ad libitum food and water.

2. Apparatus and Procedure

The apparatus was the same as that used in Experiment One. In the room where the rats were housed room lighting was provided on a 12/12 hours on/off basis with lights on at 0600h, and a temperature of 20 ± 2 degrees Celsius was maintained. The animals were brought into the laboratory and randomly assigned to running wheels, and body weight, food-intake and water-intake were recorded.

One-half of the animals in each age level were randomly assigned to one of the two experimental conditions. In condition one, rats were given 0g/day (deprivation only condition). In condition two, rats were given access to 25.0g of food (more than can be consumed in 90min) for 90min/day (meal condition). A time-limited meal was used instead of an amount-limited meal (as used in Experiment One) based upon prior studies (e.g., Routtenberg and Kuznesof, 1967) and to make food deprivation comparable across age levels. For example, a fixed amount of daily food (e.g., 15g) is a different level of food deprivation for a 6 week old rat versus a 17 week old rat. However, a time-limited meal equates opportunity to feed for all age levels. Analysis of food intake showed that the mean amount of food consumed during the 90min meal was 3.9g for the 6 and 8 week old rats and 4.2g for the 17 week old rats (not significantly different). Water was available on an ad libitum basis. Rats in both conditions were locked out of the running wheel during the 90min feeding period.

Day 1 of the experiment began with all animals in side cages and locked out of the running wheels. At noon, all remaining food was removed from rats in the 90min meal condition and side cages and trays were cleaned. The wheel entrance remained closed until the end of the 90min period, at which time all animals were given the opportunity to run until noon of the following day. All animals were removed to the side cages and the wheel entrance was closed for the 90min period on subsequent days. During this period, the rats in the 90min meal condition were fed and all dependent measures were obtained.

Dependent measures included daily wheel turns, body weight, food intake, and water intake. Body weight (grams), water intake (grams) and wheel revolutions were recorded after removal to the side cage and before meal presentation. Food intake (grams) was calculated on the difference between the amount of food given and the residual amount of food plus spillage following the 90min meal. Spillage was measured by placing clean paper toweling under the side cage at the beginning of the meal and removing it immediately after the completion of the meal minimizing the mixing of spillage with urine and feces.

Rats were removed from the experiment upon attaining 65% of initial weight (day1) or when their weight had stablized. Weight stabilization being defined as weight on day 4 of any 4-day period equal to or greater than weight on day 1 of that period. The criteria for removal and stabilization were based on daily running data and previous research findings (Epling and Pierce, 1984; Routtenberg and Kuznesof, 1967).

The present study examines the effect of a single scheduled meal versus no food in the production of excessive wheel running in activity-anorexia. The data of interest in this experiment are the development and level of running of the 90min meal subjects versus the 0g/day subjects. If excessive running is controlled by percentage weight loss alone, as suggested by previous research (e.g., Bolles, 1967), then the 0g/day subjects should increase running more rapidly than rats receiving one 90min meal/day. However, other research showing that food restricted animals increase activity levels prior to scheduled feeding periods (e.g, Boulous and Terman, 1980), indicates that the amount and pattern of activity is also related to food allocation. As a result, rats receiving a scheduled daily meal may increase activity more rapidly than rats receiving no food at all, different from Hamilton's (1969) findings reviewed earlier. As noted, this study may determine the relative importance of body weight loss versus a scheduled daily meal in the production of excessive wheel running in activity-anorexia.

C. Results

The purpose of this study was to determine whether the development of excessive wheel running observed in activity-anorexia is controlled by percentage weight loss alone or by weight loss interacting with food allocation. Graphical and statistical analyses are examined separately.

1. Graphical Analysis

An examination of the graphed individual and average data show that the number of days required to reach the highest level (peak) of running for each age level of rats is a function of initial weight differences and of food conditions within age level. These data are shown in Figures 2.1(1) (i.e., experiment 2, age level 1 - 6 weeks, condition 1 - 0g/day), 2.1(2), 2.2(1), 2.2(2), 2.3(1), 2.3(2) for individual subjects chosen at random and corresponding average of each condition in Figures 2.1(1)ave to 2.3(2)ave. For example, rats in the 17 week old group (average initial weight=352.8g) required twice the number of days to reach peak running level compared to the 6 week old rats (average initial weight=156.5g). Within the 17 week old group, rats in the 0g/day condition reached peak running level in 6 days, whereas rats in the 90min meal condition required 8 days.

The rate of weight loss for the 90min meal condition is less than the rate of weight loss for the 0g/day condition within age levels. However, in the 6 week old rats, both the 90min meal and 0g/day rats reached the 65% weight removal criterion in the same number of days (see Figure 2.H.3). Also, the rate of weight loss (grams/day) increases with age level. Importantly, this increase in rate of daily body weight loss with age level reflects a decrease in daily weight loss calculated as percentage loss of initial body weight (see Table 2.1).

To summarize thus far, rats in the 0g/day condition reached their peak running level and lost weight faster than rats in the 90min meal condition. In addition, the rate of weight loss increased with age but this increase reflected a decrease in percentage weight loss from initial body weight.

The above figures also show that the increase in daily wheel running occurs at similar rates for both 0g/day and 90min meal conditions for all age levels. As well, these figures show that the average peak running level attained was similar for the 0g/day and 90min meal conditions within age levels (with the exception of the 8 week old rats). However, a consistent difference was found when the average daily wheel turns in each food condition for each age level was calculated. Rats given a 90min meal made more wheel turns per day and in total than rats given 0g/day over the length of the experiment (see Figures 2.H.1 and 2.H.2). In summary, the rate of increase in wheel running is similar for the 0g/day and 90min meal conditions, but the level of daily activity is greater for the 90min meal condition. Importantly, body weight loss calculated either as number of grams of body weight lost per day, or as percentage body weight loss of initial weight was lower for all age levels in the 90min meal condition as compared to the 0g/day condition. However, as mentioned previously, both the 90min meal and no meal 6 week old rats reached the 65% weight criterion in the same number of days. Interestingly, both the daily and overall wheel turns in this group were higher for the 90min meal rats even though time to the weight criterion was equal. This finding provides strong evidence that one meal per day has the effect of increasing activity over and above the effect of relative body weight loss.

In conclusion, rats given a daily meal of 90min have lower daily and percentage body weight loss as compared to rats given 0g/day, but the level of daily wheel running attained is greater in the 90min meal condition for all age groups. Thus, the interaction between food allocation and percentage body weight loss is responsible for the production of excessive wheel running observed in activity-anorexia since rats receiving 0g/day lost more weight but ran less than rats receiving access to food for 90min/day.

2. Statistical Analysis

Statistical analyses were performed to assess the differential effects of the 0g/day and 90min meal conditions on wheel running and body weight over the length of the experiment for the three age levels of rats. Also, an analysis of food intake between age levels was performed, but no significant difference in food consumed during the 90min meal was found (6 week rats consumed an average of 3.9g/day, 8 week rats 3.9 g/day, and the 17 week old rats 4.2g/day). As the 0g/day and 90min meal conditions may differentially affect running level and body weight loss over the length of the experiment, trend analyses were performed. All analyses employing within subject effects were conservatively corrected employing the Greenhouse-Geisser (1959) correction for autocorrelation. Since rats in the different conditions reached the 65% weight criterion for removal from the procedure in differing numbers of days, regression techniques were employed to fit individual functions for the dependent measures and standardize the results with respect to experimental duration (cf., Epling and Pierce, 1984). Similar to Epling and Pierce (1984), data were estimated as quarters of total experimental time. Single animal regression analyses showed that the estimated data satisfactorily estimated the actual data for both the weight data (range of mutiple R=.974, P<.014 to .998, P<.001) and running data (range of multiple R=.844, P<.046 to 1.000, P<.013). The following analyses were performed on these estimated data.

Analysis of Wheel Running

An important question is whether food condition (0g/day or 90min meal) affects the amount of overall wheel running and rate of change of wheel running over the duration of the experiment. Analysis of variance of the wheel running data shows that food condition has a main effect [F(1,17)=6.83, P<.02]. The mean number of wheel turns ordered by food condition is: 0g/day, (M=2536.4) and 90min meal, (M=3271.2). Age level also has a main effect [F(2,17)=41.14, P<.001]. The mean number of wheel turns ordered by age level is: 6 weeks (M=4111.5), 8 weeks (M=2834.9), and 17 weeks (M=1549.8). Finally, there is a main effect of experimental quarter, showing a significant increase in wheel running over time in the experiment [F(1,17.7)=31.78, P<.001]. The mean number of wheel turns ordered by experimental quarter is: P1 (M=1703.8), P2 (M=2859.0), P3 (M=3465.4), and P4 (M=3523.1). Trend analysis of wheel running over experimental quarter indicated significant linear [F(1,51)=83.30, P<.001] and quadratic [F(1,51)=12.05, P<.002] components. Inspection of the data showed that for the first three quarters of the experiment running increased in a linear fashion.

However, the fourth quarter was discontinuous as running level only increased marginally. This change in rate accounts for the significant quadratic trend. In summary, these analyses can be interpreted as showing an increase in rate and level of wheel running over experimental quarters.

There is a significant interaction of age level with experimental quarter [F(2.1,17.7)=4.11, P<.033]. Trend analysis of this interaction revealed significant linear [F(1,51)=6.51, P<.014] and quadratic [F(1,51)=15.09, P<.001] components. Data inspection showed that for all age levels running was linear for the first 3 quarters (see Figure 2.4). However, for the 6 week old rats running decreased in the fourth quarter, while continuing to increase for the 8 and 17 week old rats. Despite this dropoff in running level, the 6 week old rats maintained a higher fourth quarter running level than the 8 and 17 week old rats. In summary, these analyses show that running increases over experimental quarters for the 8 and 17 week old rats, while describing an inverted U-shaped function for the 6 week old rats. Analysis of the significant three-way interaction of age level with food condition and experimental quarter [F(2.1,17.7)=6.87, P<.006] showed that this dropoff was due to the 6 week old rats receiving 0g/day.

There is also a significant interaction of food condition with experimental quarter [F(1,17.7)=14.37, P<.002]. Trend analysis of this interaction revealed significant linear [F(1,51)=38.99, P<.001] and quadratic [F(1,51)=4.00, P<.051] components. Rats in the 0g/day condition produced an inverted U-shaped function in running over the length of the experiment, while the 90min meal subjects continued to increase running level linearly over the duration of the experiment (see Figure 2.5).

Finally, to assess whether the observed differences in running could be due to differences in day 1 running level because of age differences, an analysis of covariance employing age in weeks as the covariate was carried out. No significant differences from the preceding analysis were found suggesting that differences in running were due to experimental conditions.

In summary, rats in all age levels showed significantly greater overall level and rate of increase of running in the 90min meal condition compared to the 0g/day condition. Running level significantly decreases with age level, while rate of running increases linearly and significantly over experimental quarters within age levels (except for the 0g/day 6 week old rats).

Analysis of Body Weight

If body weight loss is responsible for the differential effect of the 0g/day and 90min meal conditions on wheel running, then body weight should decline differentially across the 0g/day and 90min meal conditions irrespective of initial weight differences across age levels (see means and standard deviations in "subjects" section above). Results of an analysis of covariance controlling for initial body weight showed that there is no main effect of food condition, nor is there a significant interaction of food condition by experimental quarter. The only significant main effect is due to experimental quarter [F(1,16.5)=3049.65, P<.001], showing that body weight changed over the duration of the experiment. Trend analysis of body weight change data over experimental quarters showed a significant linear component [F(1,34)=6284.11, P<.001] such that food condition did not differentially affect weight loss and that body weight decreased in a linear fashion over the duration of the experiment. The mean amount of differential body weight loss ordered by experimental quarter and food condition is: 0g/day: P1=242.7; P2=219.4; P3=196.0; P4=172.7; 90min meal: P1=228.5; P2=207.3; P3=186.1; P4=164.9.

In order to determine the changes in body weight over time due to different initial body weight levels (i.e., age differences) and food conditions, an analysis of variance of the weight difference data was performed (e.g., weight difference1=weight day2-weight day1). Age level has a main effect on overall level of body weight loss [F(2,17)=97.57, P<.001]. The mean amount of body weight loss ordered by experimental quarter and age level is: 6 weeks: P2-P1=16.0; P3-P2=32.0; P4-P3=47.9; 8 weeks: P2-P1=21.9; P3-P2=43.8; P4-P3=65.7; 17 Weeks: P2-P1=30.0; P3-P2=60.0; P4-P3=90.0. That is, rats of different initial ages and body weight lost different average amounts of body weight over the course of the experiment. Food condition has a weak (but non-significant at the .05 level) effect on overall differences in weight loss [F(1,17)=3.19, P<.092] with the 0g/day rats showing more overall weight loss than rats in the 90min meal condition. More importantly, there is a weak (but non-significant) interaction of food condition with experimental quarter [F(2,17)=3.19, P<.092]. Inspection of the data showed that rate of weight loss over the duration of the experiment was greater in the 0g/day condition than in the 90min meal condition for all three age levels.

There is a main effect of experimental quarter, showing a significant increase in weight loss over experimental time [F(1,17)=3142.06, P<.001]. Trend analysis of weight change over experimental quarter indicated a significant linear component [F(1,34)=6284.11, P<.001] without higher order components. There is also a significant interaction of experimental quarter with age level [F(2,17)=97.57, P<.001]. Trend analysis of this interaction revealed a significant linear component [F(1,34)=385.68, P<.001] without higher order components. Data inspection showed that older, heavier animals showed a greater rate of weight loss than younger, lighter animals.

In summary, these analyses show that the rate and overall amount of body weight loss is linear over the duration of the experiment and is ordered by age level (and thus initial weight) of the rats. Older, heavier rats lost weight more quickly than younger, lighter rats. Using initial body weight as a covariate eliminated any differences in weight loss between the two food conditions. However, an analysis of variance of the weight difference data showed that rats of all age levels lost more weight in the 0g/day condition than in the 90 min meal condition.

D. Discussion

The results of this experiment showed that rats receiving 0g/day of food lost weight more quickly than rats receving a 90min meal (significance level of P<.092), but that the 90min meal group made significantly more wheel turns/day than the 0g/day group (significance level of P<.02). Therefore, the excessive wheel turning observed in this study cannot be explained by percentage body weight loss alone as suggested by previous research (e.g., Collier, 1969; Bolles, 1967). In addition, these data are in sharp contrast to Hamilton's (1969) findings which would predict that 0g/day rats would be more active than rats receiving food bulk. As the rats in the present study received food and not edible nonnutritive bulk, edible food allocation must interact with body weight loss in the production of excessive wheel running in a different manner than nonnutritive bulk.

The use of a 0g/day and a 90min food schedule allowed the separate statistical examination of body weight loss and food allocation unlike previous research (e.g., Finger, 1951; Duda and Bolles, 1963). The rate of weight loss was greater in the 0g/day condition than in the 90min meal condition (but not significant at the .05 level), and rats in the 90min meal condition ran signficantly more than rats in the 0g/day condition. In addition, as mentioned previously, both the 90min meal and 0g/day 6 week old rats reached the 65% weight criterion in the same number of days. However, both the daily and overall wheel turns in this age level were higher for the 90min meal rats than the 0g/day rats. This finding provides strong evidence that one meal per day has the effect of increasing activity over and above percentage body weight loss. Thus, it is possible to conclude that receiving a scheduled daily meal is important in the production of excessive wheel running in activity-anorexia over and above relative body weight loss.

Finally, when these data are examined graphically (see Figures 2.1(1) - 2.3(2)ave), excessive running does not develop in either the 0g/day or 90min meal conditions until body weight loss to about 80% initial weight has occurred. Therefore, it is possible to conclude that the development of excessive running observed in activity-anorexia is controlled by body weight loss interacting with food allocation as proposed by Epling and Pierce (1988).

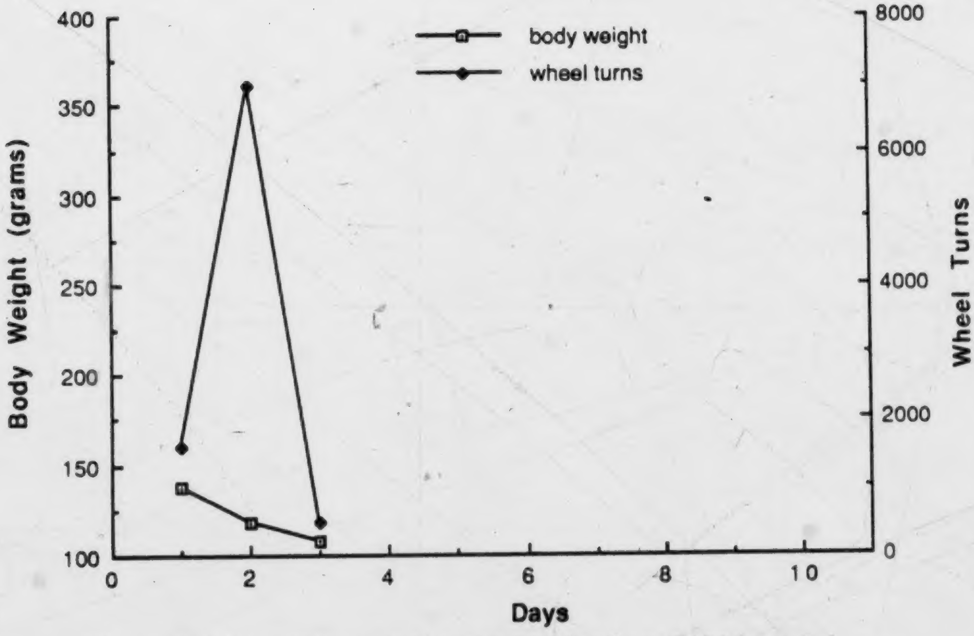


Figure 2.1(1): daily wheel turns and body weight for rat A0794 for length of experiment (age=6 weeks; meal=0g/day).

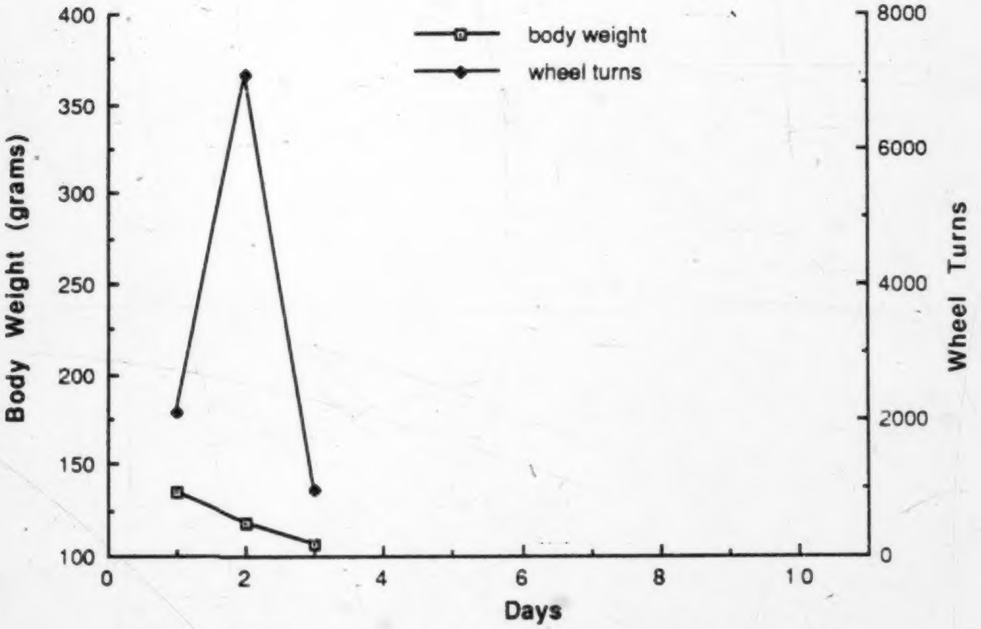


Figure 2.1(1)ave: average wheel turns and body weight for all 6 week old rats (N=4) in 0g/day condition.

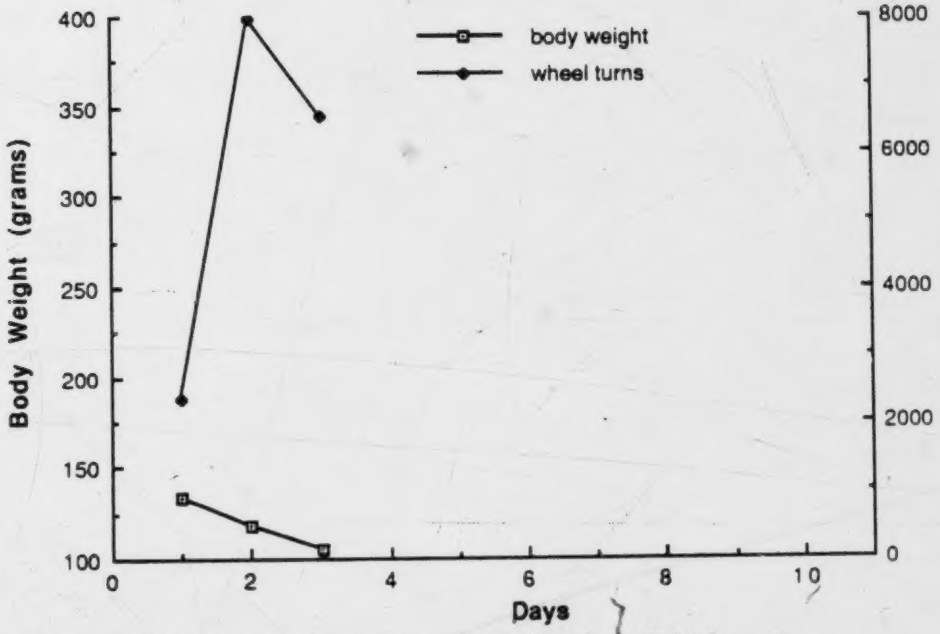


Figure 2.1(2): daily wheel turns and body weight for rat A0795 for length of experiment (age=6 weeks; meal=90min/day).

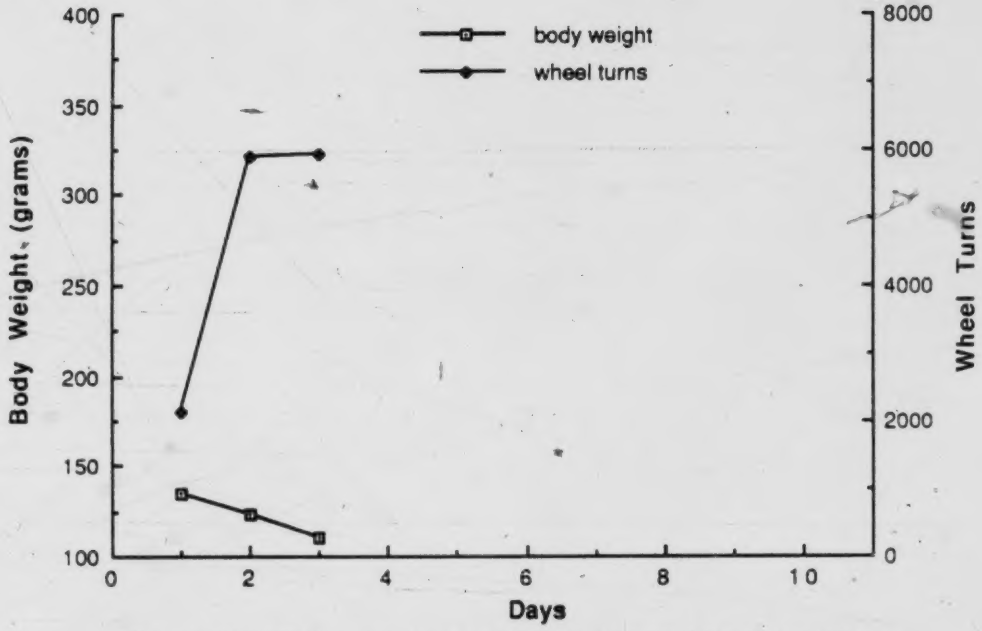


Figure 2.1(2)ave: average wheel turns and body weight for all 6 week old rats (N=4) in 90min/day condition.

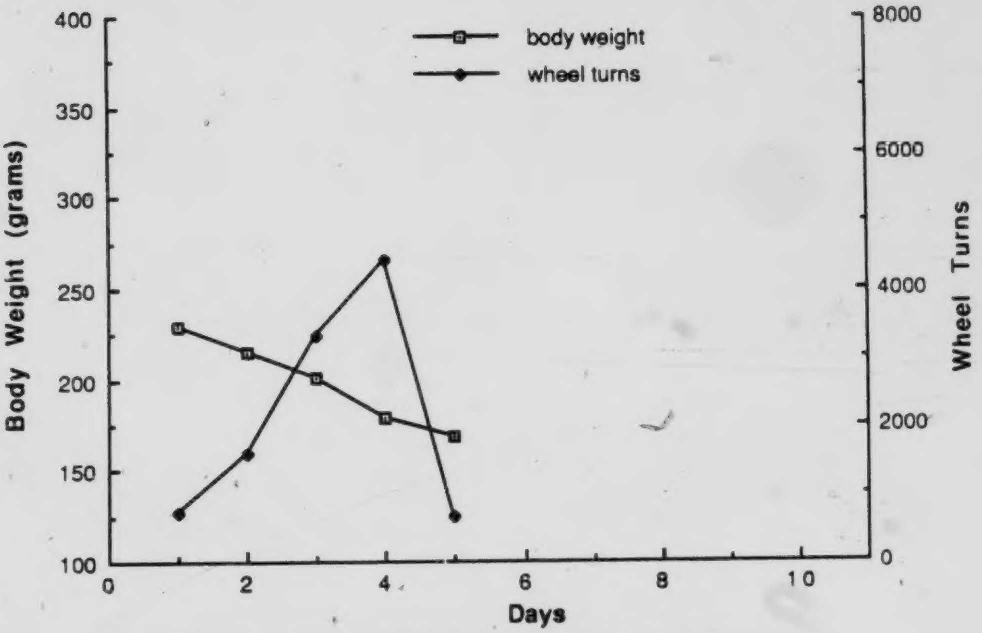


Figure 2.2(1): daily wheel turns and body weight for rat 9643 for length of experiment (age=8 weeks; meal=0g/day).

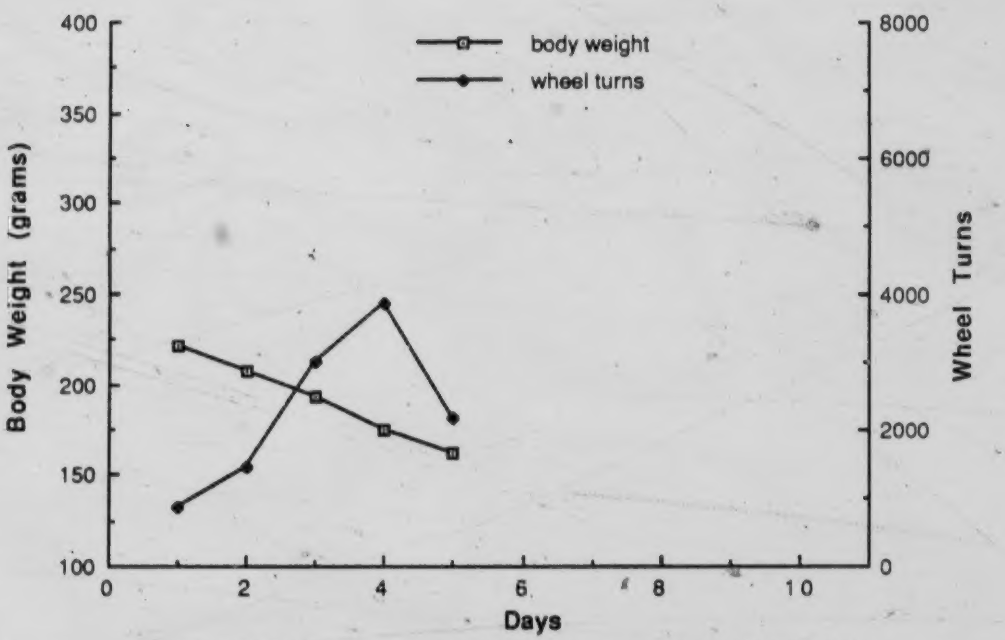


Figure 2.2(1)ave: average wheel turns and body weight for all 8 week old rats (N=4) in 0g/day condition.

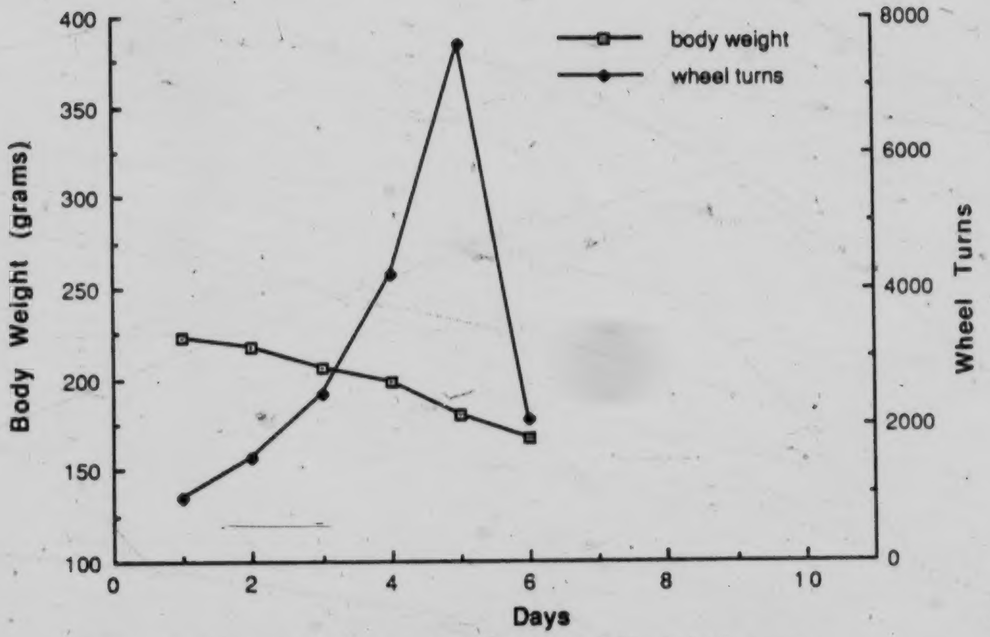


Figure 2.2(2): daily wheel turns and body weight for rat 9653 for length of experiment (age=8 weeks; meal=90min/day).

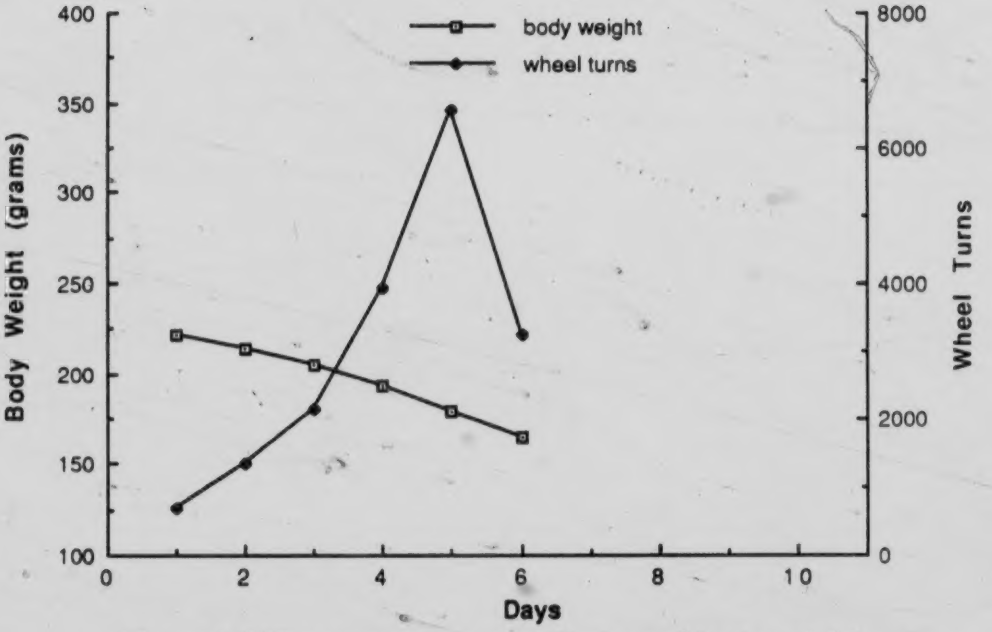


Figure 2.2(2)ave: average wheel turns and body weight for all 8 week old rats (N=4) in 90min/day condition.

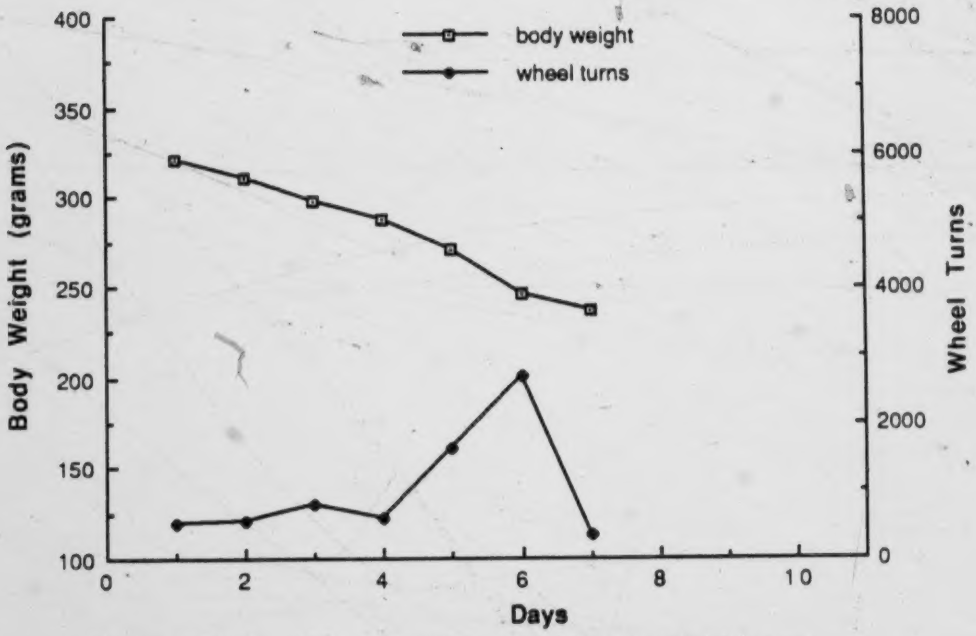


Figure 2.3(1): daily wheel turns and body weight for rat 9596 for length of experiment (age=17 weeks; meal=0g/day).

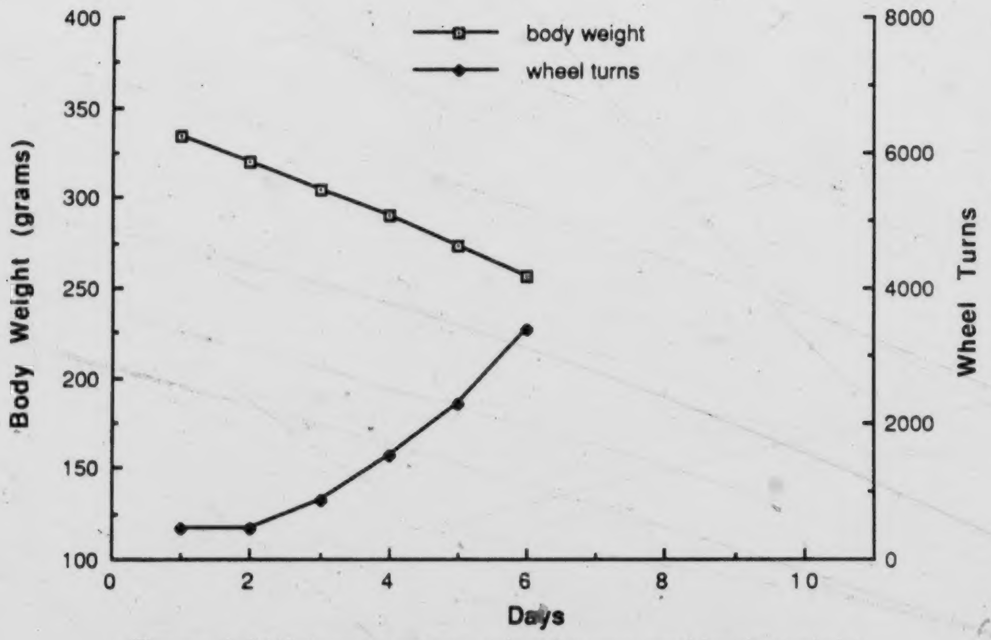


Figure 2.3(1)ave: average wheel turns and body weight for all 17 week old rats (N=4) in 0g/day condition.

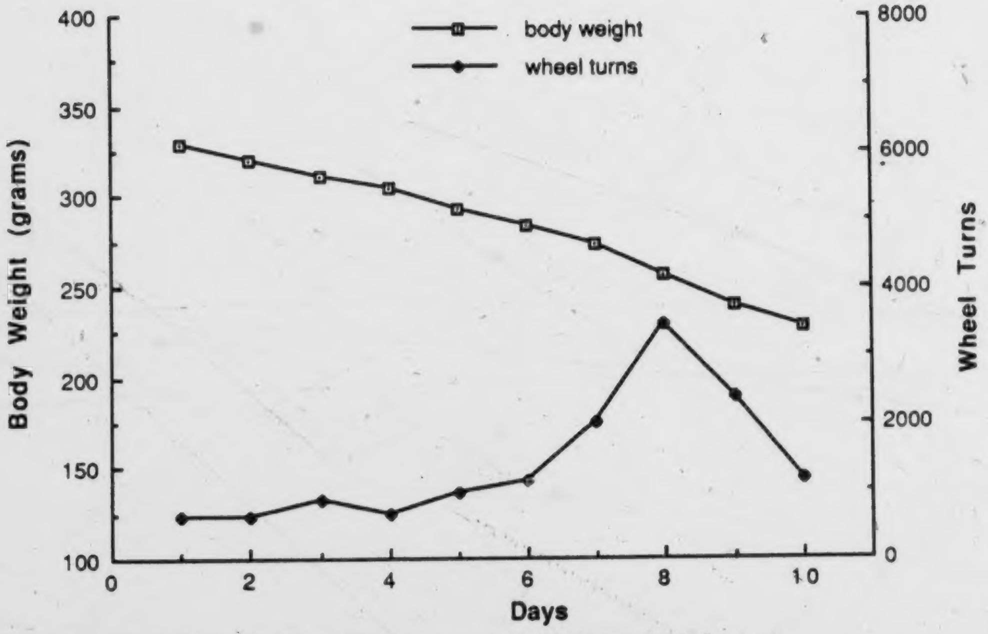


Figure 2.3(2): daily wheel turns and body weight for rat 9532 for length of experiment (age=17 weeks; meal=90min/day).

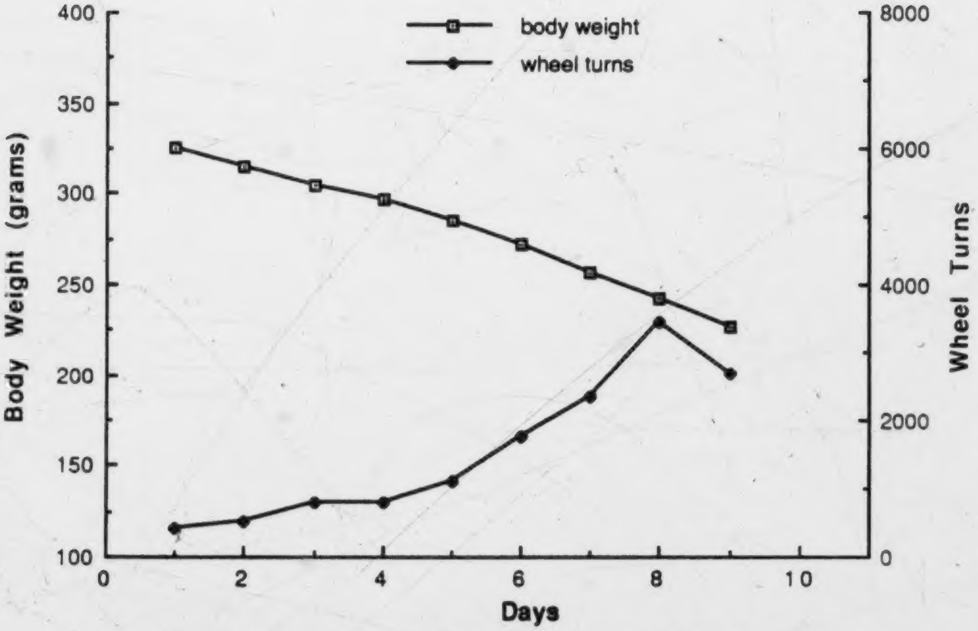


Figure 2.3(2)ave: average wheel turns and body weight for all 17 week old rats (N=3) in 90min/day condition.

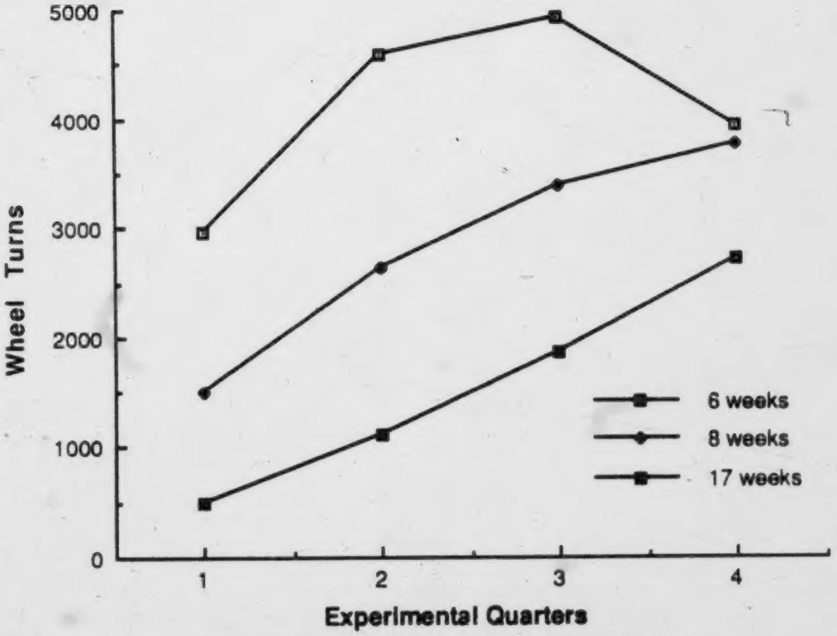


Figure 2.4: interaction of age level with experimental quarter for experiment 2.

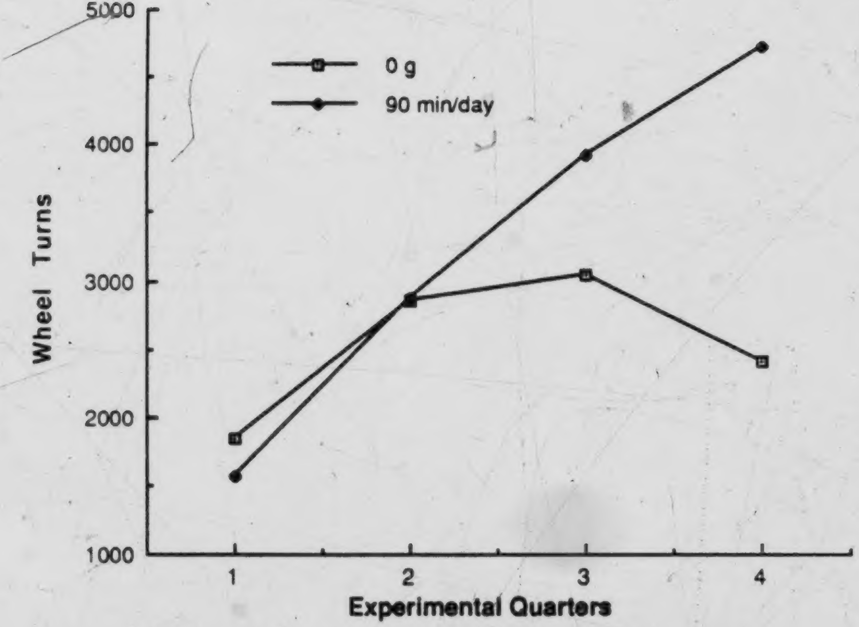


Figure 2.5: interaction of food condition with experimental quarter for all rats in experiment 2.

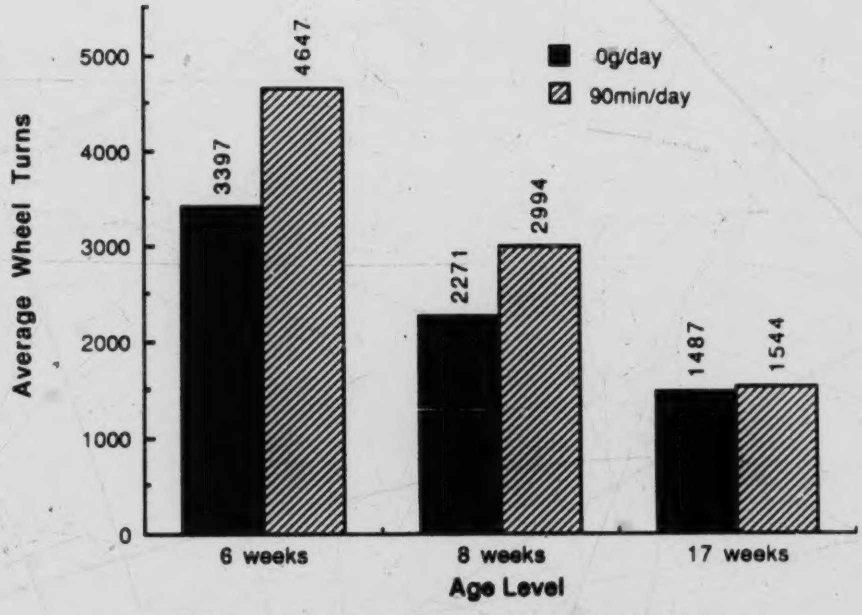


Figure 2.H.1: average daily wheel turns for each age level of rats in experiment 2.

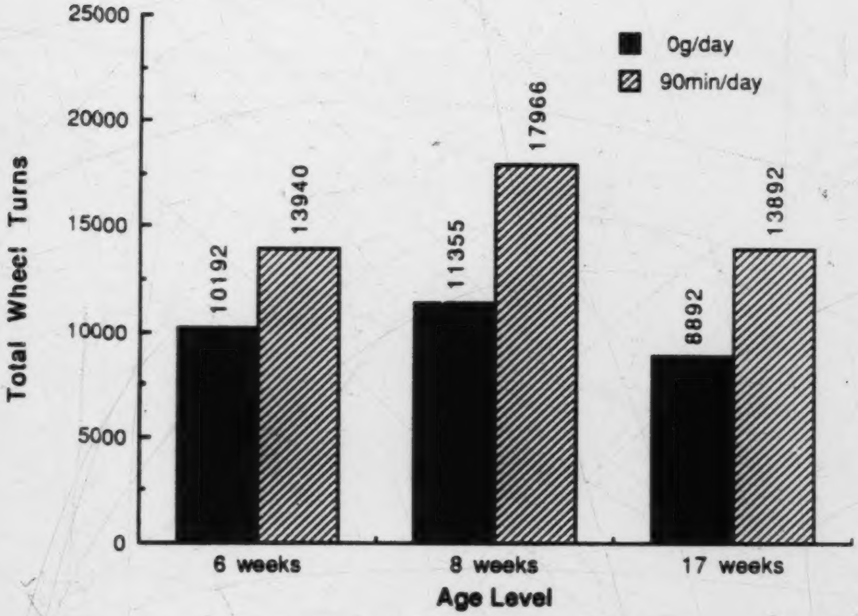


Figure 2.H.2: total wheel turns for each group of rats in expt 2.

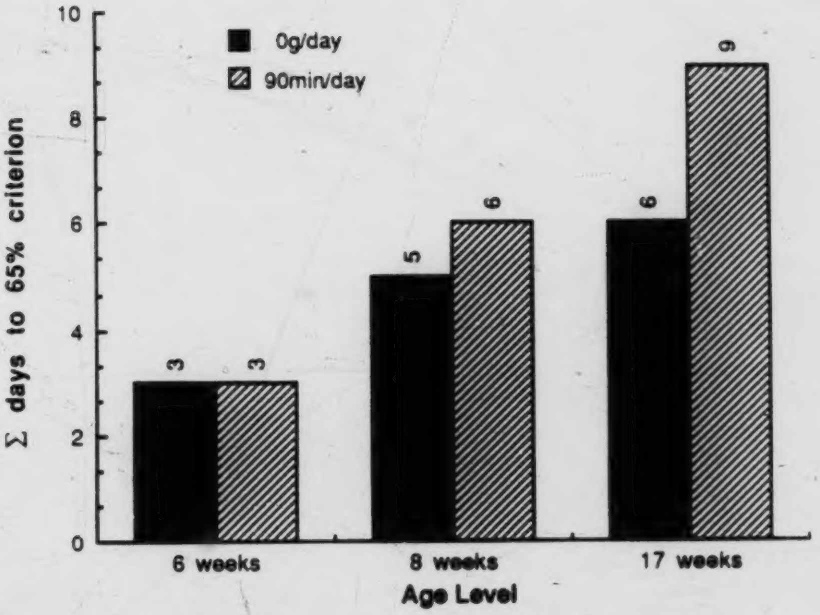


Figure 2.H.3: number of days to 65% weight criterion for each group of rats in expt 2.

Table 2.1

(A) average rate of body weight loss (g/day) and (B) percentage body weight loss from initial weight for all rats in experiment two.

Age (and food condition)	A	B
6 (0g/day)	9.7	6.2
6 (90min/day)	8.1	5.2
8 (0g/day)	11.8	4.9
8 (90min/day)	9.6	4.0
17 (0g/day)	12.8	3.5
17 (90min/day)	10.9	3.0

Table 2.2

(A) Correlation between average daily wheel turns and average body weight for 0g/day and 90min/day conditions for all rats in experiment two.

Age	0g/day	90min/day
6	.003	.725
8	.456	.535
17	.933	.894

(B) Correlation between log wheel turns and log percentage body weight loss for 0g/day and 90min/day conditions for all rats in experiment two.

Age	0g/day	90min/day
6	.039	.816
8	.727	.835
17	.845	.941

(C) Correlation between log wheel turns and log body weight for 0g/day and 90min/day conditions for all rats in experiment two.

Age	0g/day	90min/day
6	.096	.697
8	.529	.631
17	.971	.919

IV. EXPERIMENT THREE

A. Introduction

Experiment Three examined whether high activity levels in activity-anorexia, once established, are under the control of food density or percentage body weight as suggested by prior research (e.g., Collier, 1969). In this experiment, food was titrated in a manner designed to minimize weight gain or loss due to daily changes in food supply. Changes in activity level, if changes in body weight level are minimal, would suggest that established high rate wheel running is under the control of food density.

B. Method

1. Subjects

5 male JCR:LA/N-corpulent (lean) six week old rats were obtained from the Health Sciences Laboratory Animal Centre, University of Alberta, Clinical Sciences Building, Edmonton, AB. Prior to the experimental procedures the animals were individually housed and maintained on ad libitum food and water.

2. Apparatus and Procedure.

The apparatus was the same as that used in Experiment One. In the room where the rats were housed room lighting was provided on a 12/12 hours on/off basis with lights on at 0600h, and a temperature of 20 ± 2 degrees Celsius was maintained. The animals were brought into the laboratory and randomly assigned to running wheels, and body weight, food-intake and water-intake were recorded.

At the beginning of the experiment, the wheel access was opened to give rats the opportunity to run. Water was available on an ad libitum basis throughout the adjustment and experimental phase. All rats were placed on a one meal per day feeding schedule of 15g to 18g for 10 days to initiate wheel running. During this initial 10 day period, food was increased from 15g per day to 18g per day contingent upon number of daily wheel turns. When rats ran more than 6000 revolutions in a day, daily food allocation was increased to 18g for that animal.

Following the establishment of steady-state level of running (at 15g or 18g per day), all rats were placed on a feeding schedule which varied daily food allocation. The daily amount of food presented to the rats was titrated in multiples of one gram (+ or -) from the initial food value for a period of four days and then returned to the baseline amount for four days before being altered again in the opposite direction. For example, rat 9538 was exposed to the following food values for consecutive four day periods: 15, 14, 15, 16, 15, 13, 15, 17, 15, 12, 15, 18, 15, 11, 15, 19, 15, 10, 15, 20. If the baseline value of the initial 10 day food period was 18g, food was titrated in multiples of one gram (+ or -) from 18g for four day periods and then returned to the baseline amount for four days before altered again in the opposite direction (e.g., rat 9418). Feeding schedules were counterbalanced across subjects, that is, some rats began with a four day increase in daily food allocation while others began with a four day decrease in food allocation.

The feeding schedules started with small differences (+/- one gram) from the baseline value and progressed to large differences (+/- five grams) from the baseline value. Since the rats were six weeks old at the beginning of the experiment, food schedules were designed to minimize weight gain or loss at the beginning of the procedure and also to reduce systematic weight gain or loss over the duration of the feeding schedules. Figures 3.1.1 to 3.1.6 depict average wheel revolutions, range of wheel turns and body weight for each food value for rat 9538.

The resulting daily number of wheel turns represents the amount of running behavior supported by a particular meal size, if changes in activity level are not due to changes in body weight. The number of wheel turns is expressed as a function of daily food allocation for all subjects. Body weight data was also obtained to determine if variations in wheel running were due to changes in body weight rather than food allocation. The number of wheel turns is also expressed as a function of body weight for all subjects. Finally, data were also obtained for the amount of water consumed and food spillage on a daily basis.

C. Results

The purpose of this study was to determine whether high rate wheel running, once established, is under the control of body weight or food density (amount of daily food). Graphical and statistical analyses are examined separately.

1. Graphical Analysis

As the results for all subjects were similar, one rat was chosen at random and graphed. Figures 3.1.1 and 3.1.2 depict mean body weight (and standard deviation) and mean wheel turns (and standard deviation) as a function of 4 day food periods for rat 9538 for the total experiment. For clarity, these graphs are superimposed in Figure 3.1.3.

An examination of these graphs shows that, in general, wheel running increases during low food density periods and decreases during periods of high food density (see also Figure 3.1.6a). Also, there is a decline in wheel turning over repeated presentations of the 15g condition which corresponds with the increase in body weight over the duration of the experiment.

There is no apparent correspondence between body weight and changes in food amount (see Figure 3.1.6b). However, there is an overall increase in body weight over the duration of the experiment. Finally, Figure 3.1.5 depicts body weight and wheel turns for the duration of the experiment for rat 9538. This figure illustrates the lack of relationship between body weight and wheel running at the daily level, while showing an overall increasing trend in body weight and decreasing trend in wheel running.

2. Statistical Analysis

The significance of the relationship between wheel running and changes in food amount, wheel running and body weight, and body weight and food amount was assessed in the following manner. Histograms of these data were made for each rat (one rat chosen at random is depicted in Figures 3.1.6a, 3.1.6b, 3.1.6c). Figure 3.1.6a depicts mean wheel turns as a function of 4 day food periods for rat 9538. A "+" indicates a change in number of wheel turns in the "expected" direction, that is, a decrease in food amount from one food period to the next was expected to increase level of running and vice versa. If the expected result did not occur a "-" was given. Wheel running changed 17/20 times in the expected direction as predicted by change in food amount. A test for significance of a proportion (Bruning and Kintz, 1977) showed this to be significant [z=3.13, P<.002]. Figure 3.1.6b depicts mean body weight as a function of 4 day food periods for rat 9538. Decreases in amount of food was expected to result in a decrease in body weight and vice versa. Body weight changes occurred in the expected direction 10/20 times (nonsignificant). Figure 3.1.6c depicts mean wheel turns as a function of body weight in the consecutive 4 day food periods. An increase in body weight was expected to result in a decrease in wheel turns and vice versa. Wheel turns changed in the expected direction 10/20 times (nonsignificant).

In summary, similar results were obtained for all rats for all of the above comparisons (see Table 3.1). These results show that level of wheel running changed significantly in the expected direction with changes in amount of food. Wheel running did not change significantly in the expected direction with changes in body weight, nor did body weight change significantly in the expected direction with changes in food amount.

Multiple and simple regression analyses were performed to assess the differential relationships between body weight and food amount to wheel running. Multiple regression of food amount and body weight on wheel running revealed that once food amount is taken into account, body weight does not account for further variation in wheel running (see Table 3.2). Simple regression of food amount and body weight on wheel running showed that variation in wheel running was accounted for by food amount but not by body weight (see Table 3.3). Thus, significance tests of the individual coefficients revealed that variance in wheel running is accounted for by food amount and not body weight.

Finally, to assess whether changes in body weight lagged behind changes in food amount, autoregression analyses of food amount on body weight were performed for lags of 0, 1, 2, 3, 4, and 5 days for all rats. Autoregression analyses for rat 9538 revealed an increasingly significant linear relationship between body weight and changes in food amount up to a lag of 4 days [lag 0, F(1,83)=1.3, P<.106; lag 1, F(1,82)=5.2, P<.026; lag 2, F(1,81)=9.4, P<.003; lag 3, F(1,80)=12.5, P<.001; lag 4, F(1,79)=13.1, P<.001]. Similar results were found for rats 9418 and 9419 except that the most significant relationship between body weight and food amount was found at a 5 day lag. Rats 9422 and 9421 did not reveal a significant relationship between body weight and changes in food at the .05 level, but the significance level for both rats was greatest at lags of 4 and 5 days respectively. Thus, autoregression analyses revealed that for all rats the relationship between body weight and food amount was not significant at the lag 0, but became increasingly significant as number of days lagged increased up to 4 days for rats 9538 and 9422, and 5 days for rats 9418, 9419, and 9421.

In summary, regression analyses show that high rate wheel running is under the control of food density and not body weight. Tests for significance of a proportion showed that wheel running changed significantly in the expected direction predicted by changes in amount of food but not by changes in body weight. In addition, body weight did not change as expected by changes in food amount. However, autoregression analyses showed that changes in body weight lagged behind changes in food amount.

D. Discussion

The results of this experiment demonstrate that high activity levels in activity-anorexia, once established, can come under the control of food density but probably not percentage body weight loss, as has been suggested by prior research (e.g., Collier, 1969). Specifically, data analyses show that variation in wheel running was accounted for by food not body weight. Further, the lack of correspondence between body weight and wheel running was emphasized by autoregression analyses of food amount on body weight which found that body weight lagged behind changes in food amount by 4 to 5 days. In addition, attributing changes in wheel running to percentage body weight loss is difficult, given that all rats gained weight over the duration of the experiment.

The present study examined the effect of a feeding schedule which varied amount of daily food in 4 day periods alternating with a return to a baseline value for a 4 day period (see procedure). Rats were not exposed to this food schedule until a high steady-state level of running had been attained with 15g to 18g food provided (average wheel turns for the day prior to experimental day 1=8777). As expected from the results of experiment 1, this excessive level of running was attained at 82.8% of initial body weight (prior to food deprivation). Thus, rats were not exposed to the varying food schedule until excessive running was already present. As can be seen in Figure 3.1.6a wheel running declined when rat 9538 was given an amount of food greater than during the previous 4 day food period and vice versa. These findings support

Epling and Pierce's (1988) contention that "during periods of food scarcity, travel should not stop when food is infrequently contacted, ... (however) increasing contact with food would indicate a replenished supply, and travel should reduce or stop at this time (p. 480)". In summary, these data show that changes in food density (meal size) effect corresponding reciprocal changes in amount of wheel turning by food restricted rats.

In conclusion, this study showed that the control of activity during activity-anorexia is of a 2-factor nature. The excessive activity begins as a function of percentage body weight loss. However, once wheel running is excessive, statistical analyses clearly show that the amount of daily food and not body weight controls activity. In fact, once activity was excessive, weight gain did not change the sensitivity of wheel running to changes in food density.

From a foraging perspective, the rat's continued locomotor activity sensitivity to food amount (despite overall weight gain and decline in running) may be due to the unpredictability of the feeding schedules used. That is, since the rats were given increasing and decreasing amounts of food, periods of "replenished supplies" and "food scarcity" were encountered. According to Epling and Pierce (1988) and Charnov (1976), locomotor activity should not stop if food is infrequently contacted as this would decrease the animal's net gain from staying in the present patch. Since the larger food amounts (richer food patches) are infrequently contacted and therefore do not represent a continuing replenished supply, activity remained at a high level and sensitive to variations in food density.

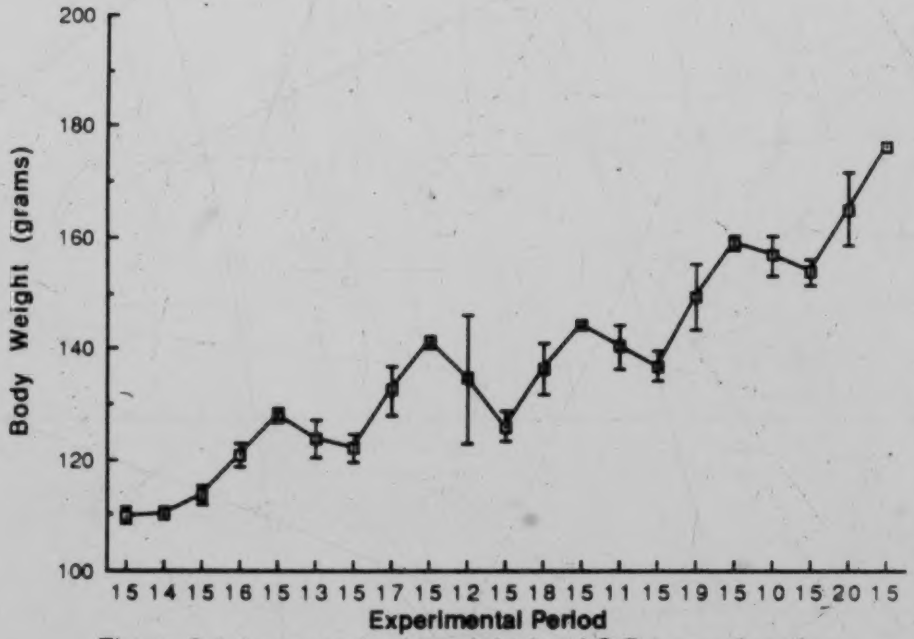


Figure 3.1.1: mean body weight (and S.D.) as a function of 4 day food periods for rat 9538 for total experiment.

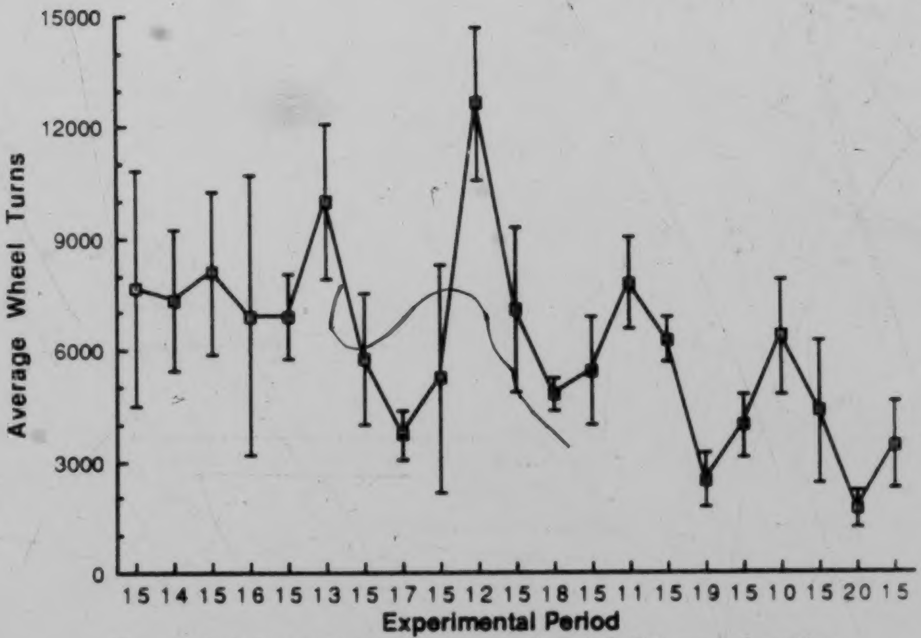


Figure 3.1.2: mean wheel turns (and S.D.) as a function of 4 day food periods for rat 9538 for total experiment.

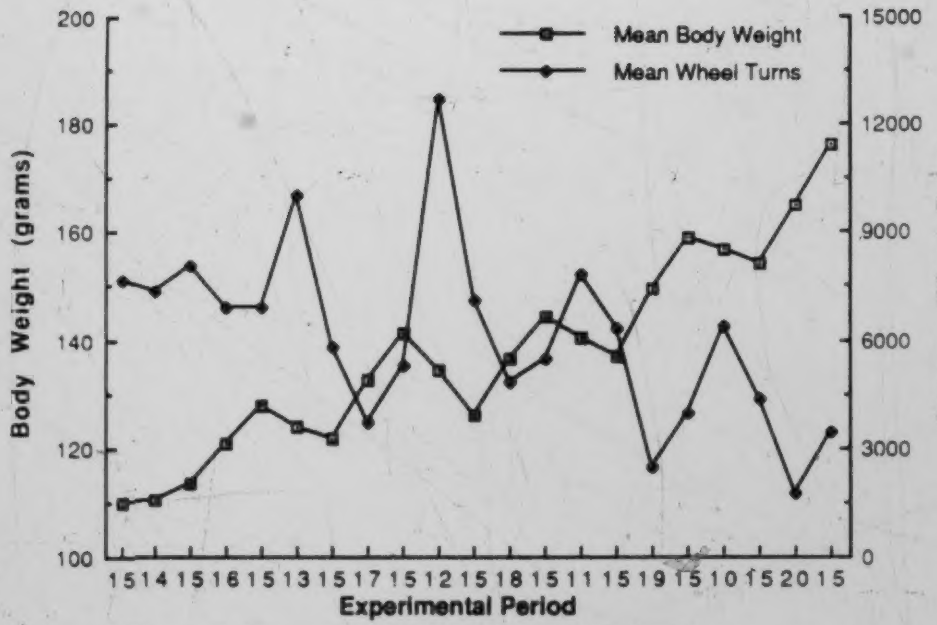


Figure 3.1.3: mean body weight and wheel turns as a function of 4 day food periods for rat 9538.

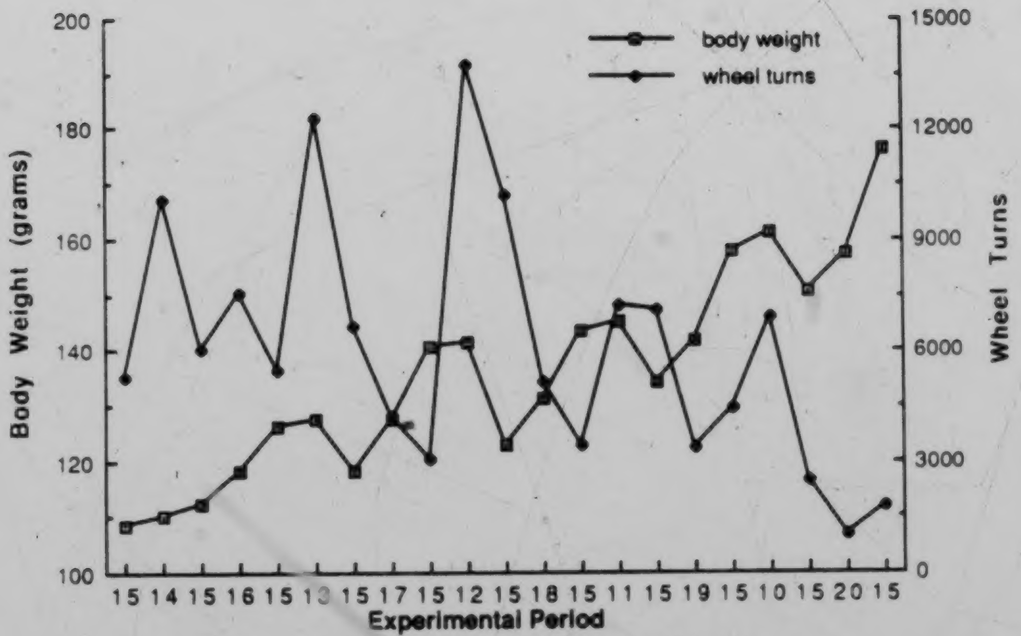


Figure 3.1.4: body weight and wheel turns on day 1 of each food period for rat 9538.

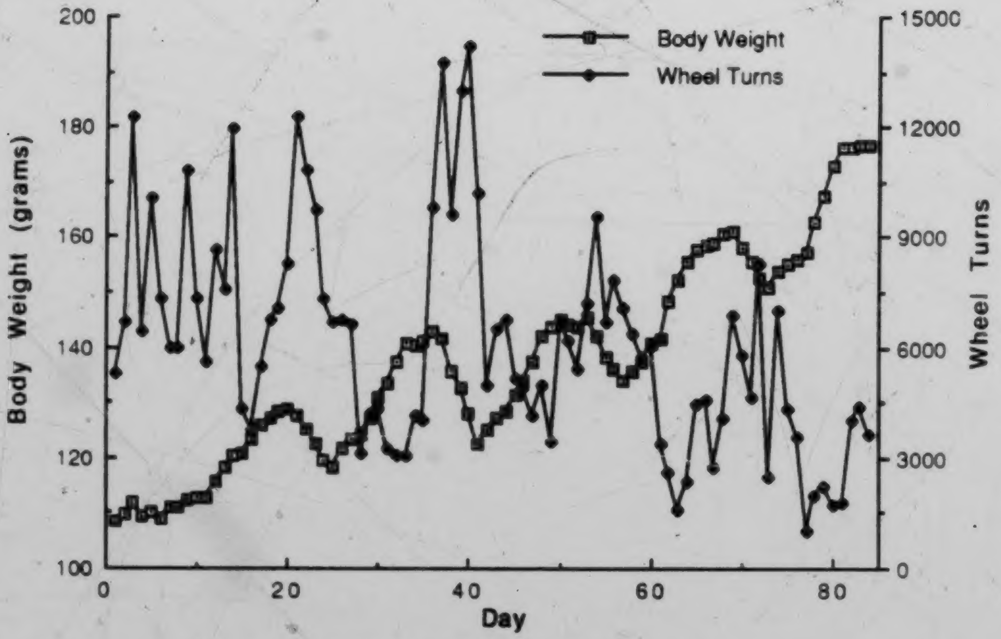


Figure 3.1.5: body weight and wheel turns for the total experiment for rat 9538.

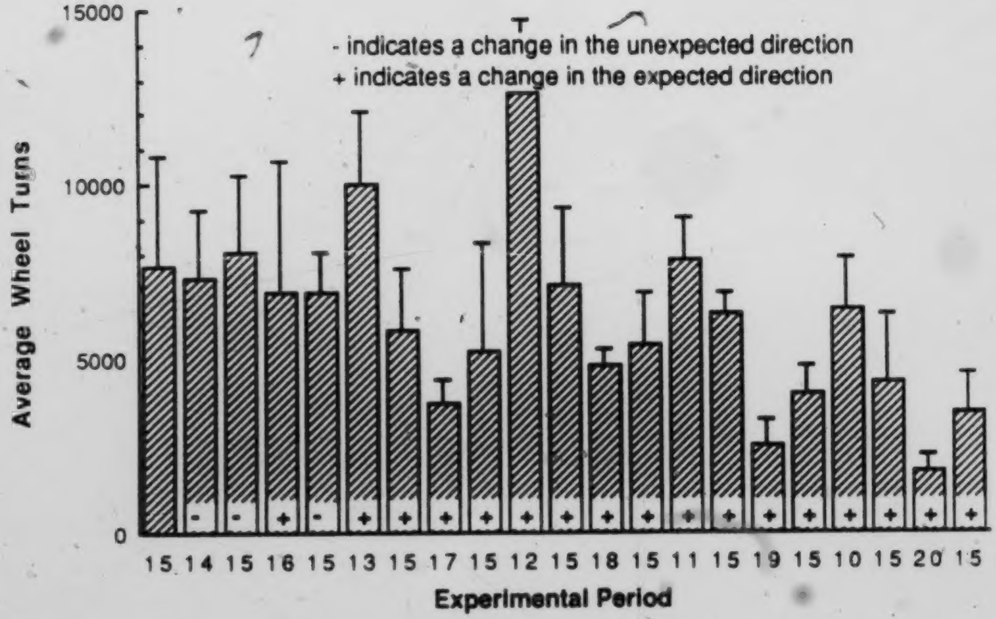


Figure 3.1.6a: mean wheel turns (and S.D.) as a function of 4 day food periods for rat 9538 for total experiment.

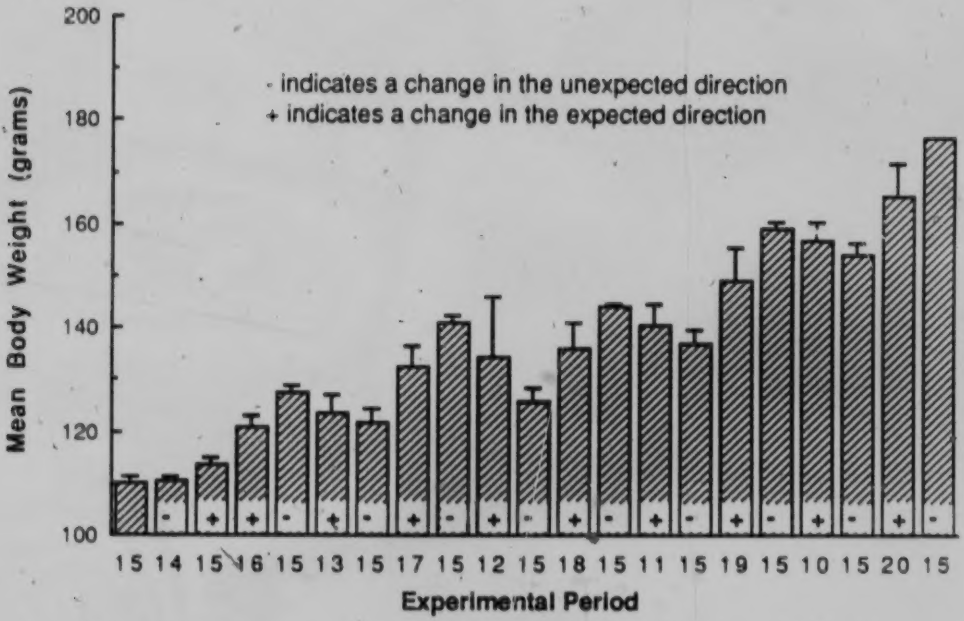


Figure 3.1.6b: mean body weight (and S.D.) as a function of 4 day food periods for rat 9538 for total experiment.

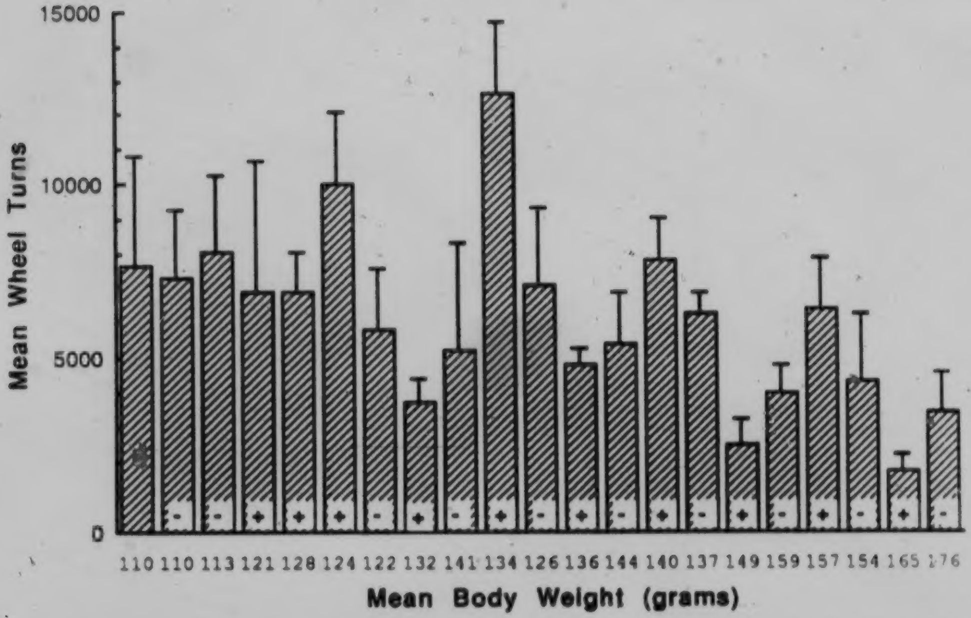


Figure 3.1.6c: mean wheel turns (and S.D.) as a function of body weight in 4 day periods for rat 9538 for total experiment.

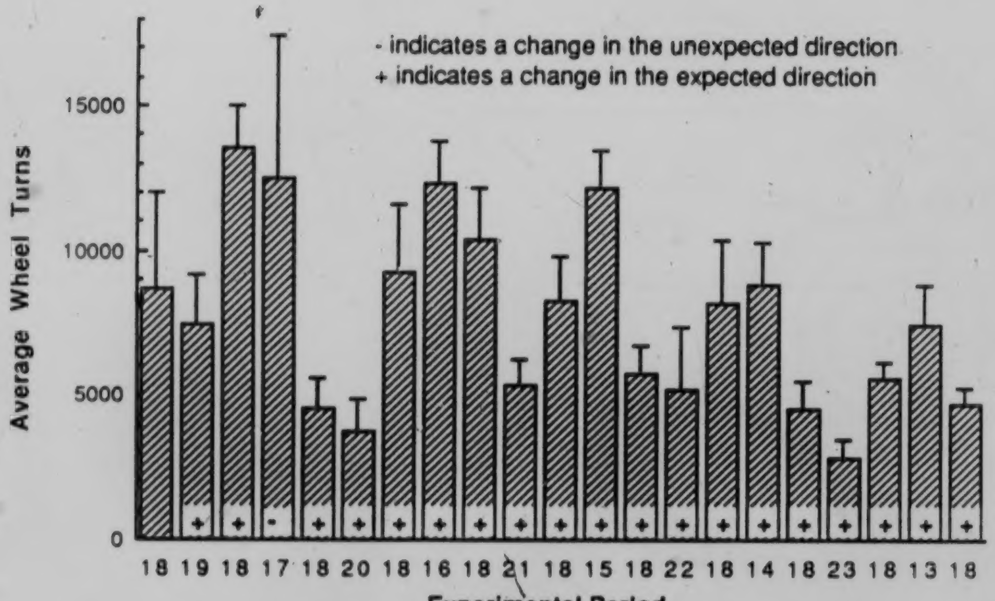


Figure 3.2.1a: mean wheel turns (and S.D.) as a function of 4 day food periods for rat 9418 for total experiment.

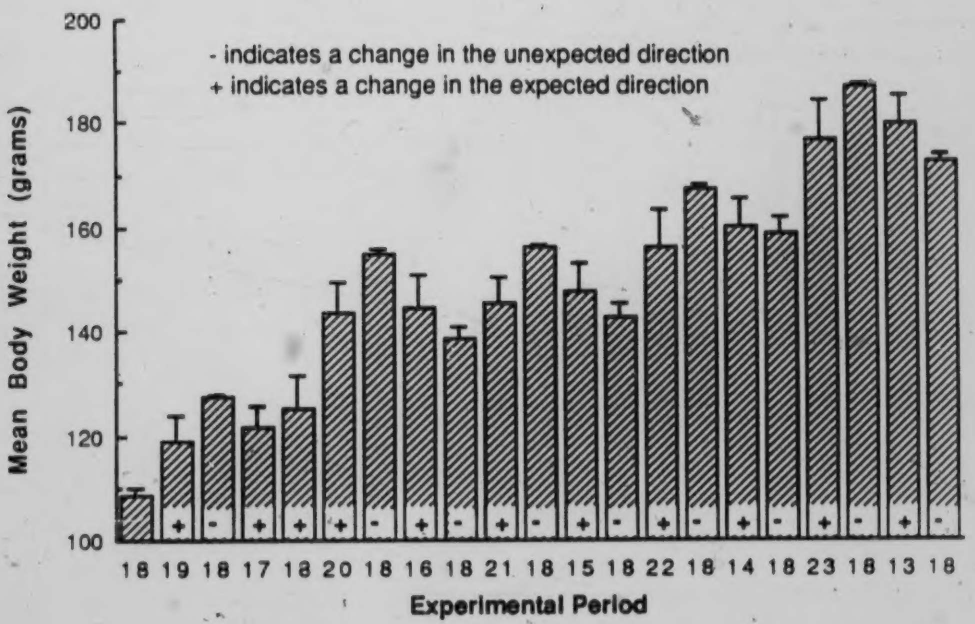


Figure 3.2.1b: mean body weight (and S.D.) as a function of 4 day food periods for rat 9418 for total experiment.

Table 3.1

Tests for significance of a proportion for (a) change in wheel turns as predicted by change in food amount; (b) change in body weight as predicted by change in food amount; (c) change in wheel turns as predicted by change in body weight for all rats in experiment 3.

Rat #	(a)	(b)	(c)
9538	3.13, P<.002	0, ns	0, ns
9418	4.03, P<.001	0.45, ns	0, ns
9419	2.96, P<.004	-0.69, ns	-0.262, ns
9421	3.13, P<.002	0, ns	0.45, ns
9422	3.58, P<.001	-0.45, ns	-0.45, ns

Table 3.2

Results of multiple regression analyses of food amount and body weight on wheel running for all rats in experiment 3.

Rat #	Variable	t-statistic	Prob>t	F	Prob>F
9538	body weight	-1.9	0.092	9.9	0.007
	food amount	-3.6	0.006		
9418	body weight	-2.5	0.037	10.0	0.007
	food amount	-3.9	0.004		
9419	body weight	-0.9	0.378	33.7	0.000
	food amount	-8.2	0.000		
9421	body weight	-0.8	0.447	5.8	0.028
	food amount	-3.0	0.014		
9422	body weight	-1.6	0.141	4.9	0.042
	food amount	-2.4	0.039		

Table 3.3

Results of simple regression analyses of food amount and body weight on wheel running for all rats in experiment 3.

Rat #	Variable	t-statistic	Prob>t	F	Prob>F
9538	body weight	-1.8	0.110	3.1	0.104
	food amount	-3.6	0.006	12.7	0.006
9418	body weight	-1.4	0.206	1.9	0.173
	food amount	-3.0	0.015	9.0	0.015
9419	body weight	0.2	0.865	0.0	0.865
	food amount	-8.2	0.000	67.5	0.000
9421	body weight	-1.1	0.307	1.2	0.195
	food amount	-3.4	0.008	11.4	0.008
9422	body weight	-1.6	0.145	2.5	0.132
	food amount	-2.5	0.036	6.0	0.036

V. EXPERIMENT FOUR

A. Introduction

Experiment Four examined the effect of naloxone upon high rate wheel running by rats. Many studies have shown naloxone to be an opiate antagonist (e.g., Brown and Holtzman, 1979; McLaughlin and Baile, 1984a; Reid, 1985; Sawynok, Pinsky and LaBella, 1979) with duration of action less than 24h (Blumberg and Dayton, 1973) (see discussion for further information). Rats were food deprived and given running wheel access until the number of wheel turns exceeded 5000 revolutions per day. At this point, animals were injected with 0.5ml naloxone (50mg/kg) and 0.5ml saline upon alternate days for a total of 20 days and wheel turns made per day recorded. Endogenous opioid involvement in maintaining high rate activity in activity-anorexia may be suggested if naloxone treatment resulted in decreased running levels.

B. Method

1. Subjects

6 male JCR:LA/N-corpulent (lean) seven week old rats were obtained from the Health Sciences Laboratory Animal Centre, Clinical Sciences Building. Prior to the experimental procedures the animals were individually housed and maintained on ad libitum food and water.

2. Apparatus

The apparatus was the same as that used in Experiment One with the addition of the drug, naloxone hydrochloride (Sigma Chemical, St. Louis, MO).

3. Procedure

In the room where the rats were housed room lighting was provided on a 12/12 hours on/off basis with lights on at 1700h, and a temperature of 20 ± 2 degrees Celsius was maintained. The animals were brought into the laboratory and randomly assigned to locked running wheels, and body weight, food-intake and water-intake were recorded.

At the beginning of the experiment, all rats were given a single 90-minute daily meal of 18.0 ± 0.3g at 1700h for a three day period and weight, food-intake and water-intake were monitored at 1700h. Wheel revolutions were recorded at 0900h, 1300h and 1700h. This period of time allowed the rats to adjust to the light cycle and running wheels. Water was available on an ad libitum basis throughout the experiment.

Subsequent to this three day period, all rats were injected with 0.5ml normal saline at 0900h on a daily basis. Daily food was preweighed and titrated from an initial value of 18.0g 90-minute/day meal to control the amount of wheel running and body weight loss for each animal. This aspect of the procedure was based upon findings by Russell et al. (1987) which showed that daily food varied between 15 to 18g/day, maintained high rate running at approximately 8000 revolutions/day over an extended period of time (139 days). Also, the results of Experiment Three show that daily wheel running is related to changes in food allocation. Taken together, these studies suggest that manipulating daily food allocation contingent on level of wheel running would allow for control over level of daily wheel running. Thus, subjects were equated for level of wheel running prior to being exposed to naloxone injections. High rate running was defined as running in excess of 5000 revolutions per day. This criterion was selected since subjects running at this level should not lose body weight when compared to subjects that run at a higher level (cf., Russell et al., 1987).

When subjects reached the high rate running criterion, they were injected with 0.5ml naloxone (50mg/kg) or 0.5ml normal saline on alternate days. This was done for each subject for a total of 20 days. Whether a subject received naloxone or saline on Day 1 was determined randomly.

The number of wheel turns per day following either naloxone or saline injection is the data of interest.

As reviewed earlier, if the initial activity observed in activity-anorexia is produced by percentage body weight loss due to food deprivation, and the endogenous opioid system is activated by food deprivation, then endogenous opioids may mediate the excessive activity observed in activity-anorexia. If naloxone (an opioid antagonist) injections result in decreased running levels, endogenous opioid involvement in maintaining high rate activity in activity-anorexia is supported. To determine this, it is necessary to show that the daily level of running obtained by the subjects is a function of the drug condition (saline or naloxone), and not a side effect of the drugs being presented on alternate days or an interaction of pairs of days and drug condition. Therefore, an analysis of variance with repeated measures must be performed with the addition of a correction for autocorrelation, since the number of wheel turns per day do not represent different episodes of running separated by a time interval.

C. Results

The purpose of this study was to determine endogenous opioid involvement in maintaining high rate activity in activity-anorexia as supported by differential wheel running to naloxone and saline injections.

The data of a single subject is given in Figure 4.1.1. Day 1 data points for body weight and wheel turns correlate with saline injection, Day 2 with naloxone injection, Day 3 saline, etc. Although the single subject data shows variability, each rat makes more wheel turns on saline injection days than after naloxone injections on the average (see Figure 4.H.1). Figures 4.S.1 and 4.S.2 also show this difference in level of average wheel turns between saline and naloxone conditions over trials for all rats.

Statistical analyses were performed to assess the differential effects of saline and naloxone injections over the length of the experiment for the six rats. Within-subject effects were conservatively corrected employing the Greenhouse-Geiser (1959) correction for autocorrelation, as all within-subject data points were collected on consecutive days.

Analysis of variance with repeated measures of the wheel running data revealed a significant main effect of drug condition (saline or naloxone) [F(1,5)=14.31, P<.013], subjects [F(5,45)=19.59, P<.001], and a weak (but non-significant at the .05 level) interaction of subjects with period (pairs of days) [F(45,45)=1.63, P<.052]. These results show that the amount of wheel running was significantly different in the two drug conditions. The mean number of daily wheel turns ordered by drug condition is: naloxone (M=4858.4) and saline (M=5819.2). The significant main effect of subjects shows that at least one of the six rats was different from the other rats in terms of overall wheel running across drug conditions and experimental duration. Figure 4.H.1 shows the variability across the six subjects in terms of overall wheel running level and the consistency in terms of differences in running level between the drug conditions.

Importantly, there is no main effect of alternate day drug presentation, nor is there interaction between pairs of days (trials) and drug condition. Thus, the effect of injecting saline or naloxone first in a trial is arbitrary. That is, drug effects are not due to the presentation order. Also, wheel running level over the duration of the experiment is shown to be consistent within the saline and naloxone conditions. Finally, there is no interaction of drug condition with subjects. That is, wheel running level of the individual rats responded similarly to the naloxone and saline conditions as shown in Figure 4.H.1.

In summary, these analyses show that wheel running level over the duration of the experiment is ordered by drug condition. Although there were differences in overall running level across rats, all subjects made fewer wheel turns in the naloxone condition compared to the saline condition.

D. Discussion

Data analysis showed that number of daily wheel turns was a function of drug condition (P<.013). These results support endogenous opioid involvement in maintaining the high rate activity observed in activity-anorexia as suggested by Epling and Pierce (1988). Some caution is required in assessing these results as opiate antagonism by naloxone has been cited by Sawynok, Pinsky and LaBella (1979) as a "necessary but not sufficient criterion for invoking the mediation of a response by an endogenous opiate (p.1621)".

The dose level of 50mg/kg of naloxone used in the present study is a high but non-toxic dose (Blumberg and Dayton, 1973). Sawynok, Pinsky and LaBella (1979) note that higher dose levels of naloxone are often used than is required to obtain a desired behavioral effect since there are various forms of endogenous opioid receptors and high concentrations of naloxone are needed to block these receptors (cf., Lord, Waterfield, Hughes and Kosterlitz, 1977; Jacquet, Klee, Rice, Ijima and Minamikawa, 1977; Gillan, Paterson and Kosterlitz, 1978).

Dose levels of naloxone similar to that employed in the present study have been shown to have agonistic effects similar to morphine (e.g., McMillan, Wolf and Carchman, 1970; Pinsky, LaBella, Havlicek and Dua, 1978). For example, Blumberg and Dayton (1973) report that in rats a dose of 50mg/kg, naloxone causes restlessness and salivation. At higher dose levels, Pinsky, LaBella, Havlicek and Dua (1978) and Dingledine, Iversen and Breuker (1978) report seizure activity in the rat. Importantly, there are no other side-effects of naloxone at high (or low) narcotic antagonistic (up to 50mg/kg) doses in rats other than the ability to modify the effects of a variety of non-opiate drugs (cf., Blumberg and Dayton, 1973; Sawynok, Pinsky and LaBella, 1979). Thus, the effects observed in the present study are not attributable to non-specific effects of naloxone on behavior. Finally, the effects of high concentrations of naloxone on behavior has been suggested to be due to gamma-aminobutyric acid (GABA is a major inhibitory transmitter in the brain) antagonistic activity (Sawynok, Pinsky and LaBella, 1979). However, the interaction of naloxone and GABA receptors is reported at dose levels of more than 50mg/kg (Blumberg and Dayton, 1973; Dingledine, Iversen and Breuker, 1978). As the dose level employed in the present study was not greater than 50mg/kg, GABA antagonist action by naloxone is not responsible for the observed results.

The use of a 50mg/kg dose must be evaluated in terms of onset of drug effect and length of drug action. Further data analyses showed that in the 4 hour period immediately after injection, the rats made more wheel turns following naloxone (1314.4) than after saline (1274.9) injections (not significant at the .05 level). During the second 4 hour post-injection period, the rats made more wheel turns in the saline (1527.9) than the naloxone (1421.7) condition (not significant at the .05 level). Wheel turning was not significantly different between the conditions until after 8 hours post-injection (naloxone=2122.3; saline=3016.4; $t(5)=9.0$, $P<.001$). This delay in effect cannot be explained as a result of delayed drug action as studies have shown that naloxone acts within 1-2min post-injection (Blumberg and Dayton, 1973) and reaches peak levels in brain tissue and serum at 15min post-injection (Tepperman, Hirst and Smith, 1983). Therefore the delayed effect of naloxone must be explained as a function of length of drug action or effective concentration of drug action.

As mentioned previously, naloxone is considered an agonist at a concentration of 50mg/kg (McMillan, Wolf and Carchman, 1970). However, naloxone has a serum half-life in the rat of 40min (Tepperman, Hirst and Smith, 1983) to 58min (Blumberg and Dayton, 1974). Thus, the dose level administered in the present study would be metabolized to typical antagonist concentrations after more than 4 to 6 hours post-injection. Typical antagonist levels range from .04mg/kg (Schnur and Raigoza, 1986), 0.15mg/kg (Shido, Nagasaka and Noda, 1986), 0.4mg/kg (Schnur and Hang, 1987), to 2mg/kg (Walker, Berntson, Paulucci and Champney, 1981), although the latter's results indicate a delayed effect by naloxone. Therefore the results of the present study suggest that once naloxone has been metabolized to an effective low concentration it operates in an antagonistic fashion and reduces endogenous opioid supported activity.

These data suggest that naloxone's agonist and antagonist properties may be the result of a single mechanism operating in a dose-related fashion as has been suggested for the biphasic effects of morphine by Schnur and Raigoza (1986). That is, naloxone has agonistic effects at high doses and antagonistic effects at low doses. However as naloxone has a short half-life, both effects can be examined as the serum and brain levels decrease. Thus, naloxone may have biphasic effects on behavior which are opposite to that of morphine elicited behavior. This possibility requires further investigation and would require post-injection monitoring in 15min intervals to assess local changes and overall trends in activity.

In summary, naloxone decreased the level of high rate wheel turning in activity-anorexia in a manner consistent with endogenous opioid involvement. The finding that naloxone operated in a dual-action or biphasic manner, initially agonizing then antagonizing the high rate activity enhances the validity of this contention. In addition, these data suggest that the effect of naloxone may, like morphine (Schnur and Raigoza, 1986), be the observable results of a single dose-related mechanism. This possibility lends additional support to endogenous opioid involvement in high rate wheel turning in activity-anorexia.

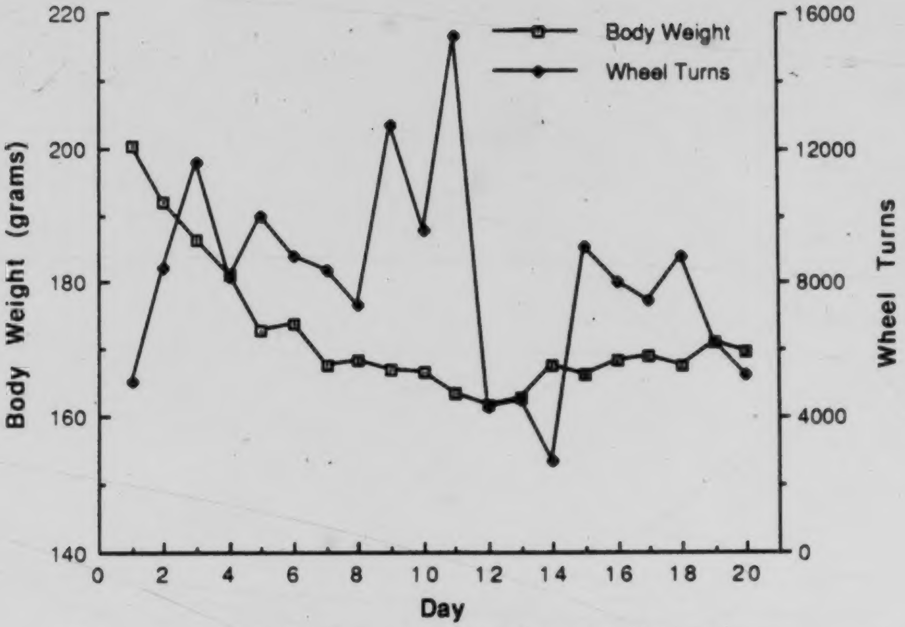


Figure 4.1.1: wheel turns as a function of saline and naloxone injections for rat 9122 (plus daily body weight).

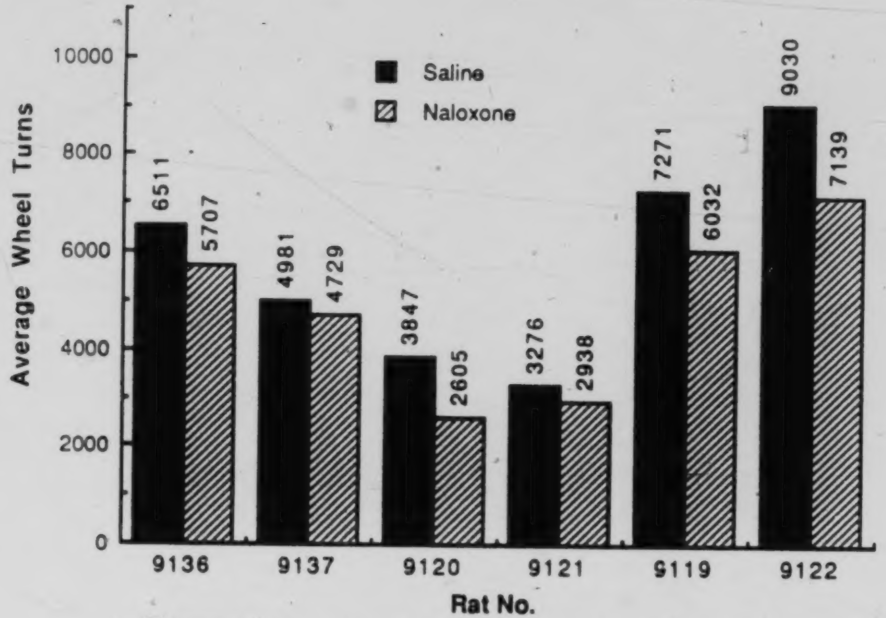


Figure 4.H.1: average wheel turns in saline and naloxone conditions for all rats in experiment 4.

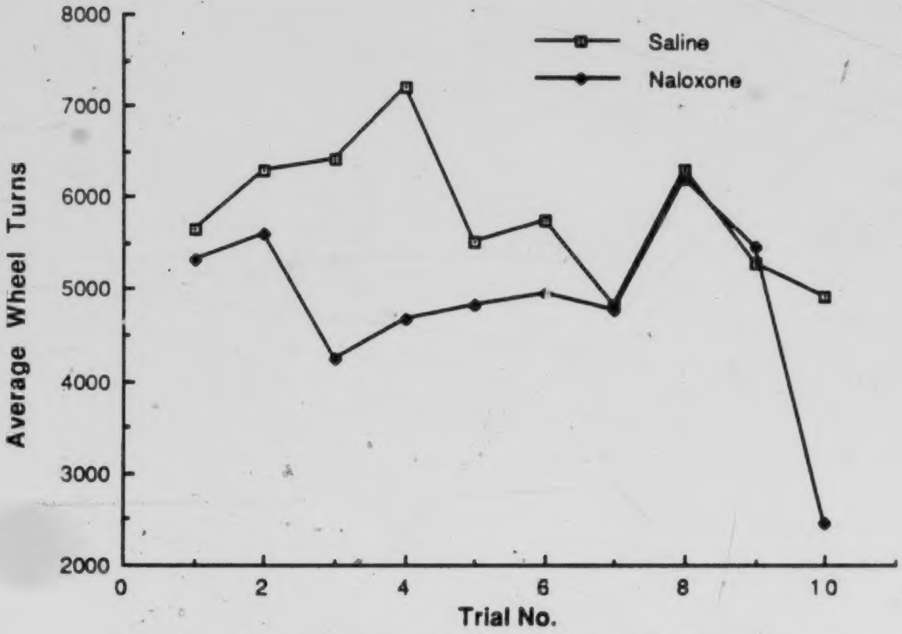


Figure 4.S.1: average wheel turns in saline and naloxone conditions over trials for all rats in experiment 4.

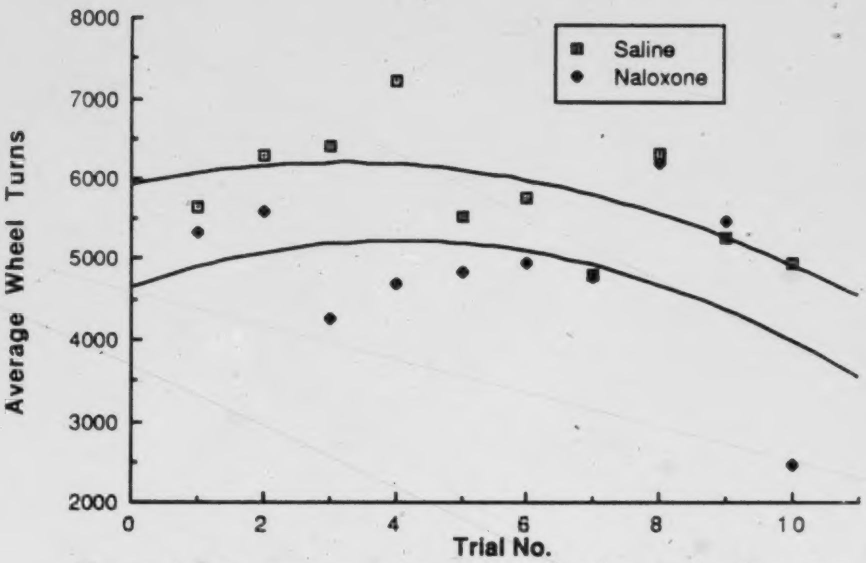


Figure 4:S.2: average wheel turns in saline and naloxone conditions over trials for all rats in experiment 4.

VI. GENERAL DISCUSSION

The present experiments were designed to identify those factors that control wheel running by rats in the activity-anorexia paradigm described by Epling and Pierce (1988). Briefly, the first and second experiments showed that wheel running increases to excessive levels as body weight declines. The second and third experiments demonstrated that once established, high-rate wheel running is a function of food allocation. Thus, the wheel running observed in activity-anorexia is controlled by two processes. Running initially increases as body weight declines, but following this increase it becomes sensitive to changes in food allocation. Finally, the fourth experiment suggested that high-rate running produces endogenous opioids which maintain activity at excessive levels.

Experiment One provided support for Collier (1969) and Bolles (1967) and Duda and Bolles (1963) contention that food deprivation results in body weight loss that produces an increase in wheel running activity. As mentioned earlier (see introduction), studies examining the effects of body weight loss and meal schedule on activity have not determined the differential effects of these two factors. The results of Experiment One do not completely differentiate between body weight loss and scheduled food allocation, in the production of high rate activity, since the size of the meal was limited to 15g. However it is important to note that food allocation in this study was not time-limited. Thus, all rats were able to consume the entire meal. Sedentary controls maintained body weight on 15g, whereas the experimental rats progressively lost weight and increased wheel turning over days. In summary, this experiment showed that body weight loss induced by moderate food restriction and activity wheel access is sufficient for the development of excessive wheel running observed in activity-anorexia.

Experiment Two was designed to examine the differential effects of body weight loss and meal schedule upon the development of excessive activity. Wheel running by animals getting one 90min meal per day was compared to revolutions produced by rats that were on total deprivation (i.e., no meals). Not surprisingly, rats on total deprivation lost body weight more quickly than rats receiving a 90min meal. Importantly however, rats receiving food made significantly more wheel turns per day compared to unfed rats. Excessive wheel running does not occur for either group of rats until sufficient body weight loss has occurred (to about 80% initial weight). In summary, this experiment showed that the development of excessive wheel turning in activity-anorexia is controlled by body weight loss, but that scheduling one meal per day induces even more activity.

The greater amount of activity in the 90min meal rats compared to the deprivation alone group may be due to an increase in activity prior to the scheduled time of feeding. Such "anticipatory activity" is well documented in rodents (e.g., Boulous, Rosenwasser and Terman, 1980; Richter, 1922). However, Kanarek and Collier (1983) showed that as meal frequency is increased but total feeding time held constant, level of wheel running decreased. Thus, the present results may be support for an anticipatory "circadian" mechanism (Honma, von Goetz and Aschoff, 1983) controlling wheel running determined by the single daily feeding period. Additional evidence for such an anticipatory mechanism may be inferred from Kanarek and Collier's (1983) study as lower running levels in the two 30min and four 15min meal groups may represent disruptions of a 24 hour circadian rhythm. Unfortunately, Kanarek and Collier (1983) did not provide data regarding number of wheel turns preceding or following food presentation on the different feeding schedules. Such data would have been valuable in determining circadian involvement.

Alternatively, the increased level of wheel running in the rats fed once per day may represent schedule-induced behavior (Falk, 1971, 1977; Levitsky and Collier, 1968). Epling, Pierce and Stefan (1983) reviewed data which suggested correspondence between schedule-induced wheel running and the high rate wheel turning seen in activity-anorexia. In brief, Epling et al. (1983) point out that schedule-induced behavior increases as a monotonic function of food deprivation within long food intervals (e.g., 23h), and that the pattern of wheel running is ordered by food presentation. Also, other adjunctive behaviors such as preening or polydipsia do not occur when the availability of a running wheel makes excessive activity possible. However, if Kanarek and Collier's (1983) wheel running data was schedule-induced, then the level and pattern of activity should be ordered by food allocation. That is, wheel running should be distributed systematically within the inter-meal interval and possibly increase with number of meals. Alternatively, the 23h inter-meal interval may be a critical determinant in the production of excessive running in a similar fashion as the use of 45mg food pellets and a fixed-interval food schedule of up to 120-180sec is to the production of adjunctive drinking (Falk, 1966, 1977). Nonetheless, rats in the four

15min meal condition ran less than rats in the two 30min condition which ran less than rats in the one 60min condition. Also, total food intake increased with number of meals. On balance, it seems more likely that the additional feeding opportunities disrupted circadian mechanisms rather than increasing schedule-induced running. Further research detailing the temporal distribution of wheel running under different meal conditions would be useful in differentiating between these hypotheses.

Finally, Experiment Two examined running as a function of meal or no meal across three age levels. Body weight varied with age in increments of approximately 100g from the 6 week to 8 week group and the 8 week to 17 week group. Campbell, Teghtsoonian and Williams (1961) have shown that rate of weight loss (as a percentage of original weight) is greatest for young (light) rats and slowest for older (heavier) rats. Additionally, running wheel activity is higher for younger (lighter) animals. Initially, 6 week old rats were used in experiment two, however, these animals only survived 3 to 4 days in the protocol. Subsequently, 8 and 17 week old rats were used to more fully investigate the differences between the no meal and 90min meal conditions.

Results were consistent across all age levels, with all no meal rats losing more weight and running less than 90min rats. Interestingly, *daily* running level significantly decreases with age level in both conditions while total wheel running to the 65% weight criterion does not(see Figures 2.H.1 and 2.H.2). However, an important factor in assessing the importance of total running is that the older rats took more days to reach the criterion (see Figure 2.H.3). Thus, daily wheel running rate which directly relates to rate of percentage weight loss reflects activity level differences between the age levels. The most important finding in this study was that both the daily and overall wheel turns in the 6 week rats were higher for the 90min meal rats even though total time to criterion was the same for both the no meal and meal rats. This finding supports the conclusion that one meal per day has the effect of increasing activity over and above body weight loss.

To summarize thus far, Experiments One and Two determined that body weight loss produced an increase in wheel running activity. Further, Experiment Two determined that body weight loss interacts with food allocation to produce significantly more wheel running than body weight loss alone. However, as noted previously, high rate activity does not occur in either the meal or no meal condition until percentage weight loss (to about 80% initial weight) has occurred. Overall, it appears that the initial running in the activity-anorexia paradigm is primarily controlled by body weight loss but meal schedule also has an effect. Providing one meal per day significantly increases running when compared to deprivation alone. Experiment Three was designed to assess the effects of changes in food density upon established high rate running activity.

The results of Experiment Three showed that high running levels observed in activity-anorexia are under the control of food density and not percentage weight loss as suggested by prior research (e.g., Collier, 1969). Specifically, data showed that changes in meal size resulted in immediate changes in amount of wheel running by rats. As daily food amount increased running decreased and as food ration was reduced activity went up. This reciprocal relationship between food allocation and activity held even though body weight was increasing over experimental days.

In summary, Experiments One through Three showed that the control of wheel running in activity-anorexia is of a two-factor nature. Activity begins as a function of percentage body weight loss (although it is also affected by meal schedule) but once excessive, the amount of daily food and not body weight controls activity.

The results of these experiments may be interpreted from a foraging perspective. The "decision" to start a migration should be determined by frequency of contact with prey items and by internal cues arising from weight loss. However, once started locomotor activity should not stop if food is infrequently contacted since intermittent contact does not represent a replenished food supply (Charnov, 1976; Epling and Pierce, 1988). Continued high rate activity would ensure that the animal would not stay in the present patch longer than the net gain of doing so warrants. Thus, this experiment may be representative of rat's natural foraging behavior.

Finally, the amount-limited meal schedule used in Experiments 1 and 3 may be more "ecologically valid" (Kamil and Yoerg, 1982) than the typical "time-limited" meal schedule used in Experiment 2 (cf., Routtenberg and Kuznesof, 1967). Once a food source (e.g., grain) is contacted in the natural environment, it is not removed (90min) afterwards. Removing food adds another "artificial" condition to the experiment making it less ecologically valid (Vaughan and Herrnstein, 1987). A rat given a fixed amount of food may consume the entire amount in one meal or in the typical 8-10 meals in 24hr observed in free-feeding rats (Richter, 1927). Thus, it is the subject and not the researcher which initiates and terminates feeding in these studies.

Experiment Four was performed to assess a possible physiological mechanism that may link the motivational value of running and eating. In particular, Epling and Pierce (1988) proposed that the endogenous opioid system mediates between locomotor activity and food intake in activity-anorexia once high activity levels are established.

Many studies have shown that endogenous opioids are increased by exercise (e.g., Amir, 1982; Walker, Berntson, Paulucci and Champney, 1981) and food deprivation (e.g., Brands, Thornhill, Hirst and Gowdey, 1979; Reid, 1985). Taken together, these studies and the literature regarding food deprivation and activity suggest that endogenous opioids modulate the excessive activity seen in activity-anorexia. The results of Experiment Four support such an endogenous opioid hypothesis since injections of the opiate antagonist naloxone significantly decreased high rate activity of food deprived rats compared to activity following saline injections.

The delayed inhibition of endogenous opioid mediated activity by naloxone in the present study seems in conflict with the fast action of naloxone after injection found by others (e.g., Tepperman, Hirst and Smith, 1983; Blumberg and Dayton, 1974). An analysis of dose concentration effects showed this delayed effect was due to the dose level employed (e.g., McMillan, Wolf and Carchman, 1970). At 50mg/kg naloxone is considered an opiate agonist (e.g., McMillan, Wolf and Carchman, 1970), however naloxone is quickly metabolized to antagonist concentrations due to its short serum half-life (e.g., Blumberg and Dayton, 1974). In fact, naloxone's apparent biphasic action in the present study - initially agonizing then antagonizing high rate activity - enhances the conclusion of endogenous opioid involvment in activity-anorexia. It is well known that morphine operates in a similar (but opposite) dual-action manner, initially inhibitory at high doses and later, excitatory at low doses (Schnur and Raigoza, 1986; Seevers and Deneau, 1962). As with naloxone in the present study, the low dose effects of morphine are observed after initially high serum levels of the drug from a single high dose are metabolized to lower levels (Schnur and Raigoza, 1986). Thus, it appears that naloxone and morphine have opposite effects at high and low doses. In addition, when naloxone is used to antagonize morphine-elicited sedation or hyperactivity the opposite behavioral process is observed (Schnur, 1985). These findings taken together with the present data, provide strong support for Epling and Pierce's (1988) claim that the endogenous opioid system is involved in the maintenance of high rate activity in activity-anorexia.

Further research using lower doses of naloxone that are known to be opiate antagonistic (cf., Shido, Nagasaka and Noda, 1986) would reinforce the above conclusion. That is, the delay of naloxone's effect on high rate activity could be eliminated by using a lower dose. Also, a study which used morphine rather than naloxone may further substantiate endogenous opioid involvement in the high rate activity observed in activity-anorexia. Morphine in a 1mg/kg dose causes an immediate increase in activity in non-anorexic rats, while higher doses (3.2, 10 and 32mg/kg) produce an initial dose-related decrease in activity followed by a delayed increase over baseline wheel running levels (Vasko and Domino, 1978). An increase in activity over high running levels observed in activity-anorexia using a 1mg/kg dose of morphine would support the claim that the endogenous opioid system is involved in the maintenance of high rate activity. Higher doses of morphine given to rats running at a high rate may produce an initial decrease in activity, but the subsequent increase in locomotor activity may be greater than that observed in non-anorexic rats given similar doses lending additional support to the above claim.

In conclusion, the present research extends Epling and Pierce's (1988) theory of activity-anorexia by providing evidence of two-factor control of wheel running. Percentage weight loss and meal schedule appear to initiate excessive levels of wheel running. However, once established, wheel running is apparently under the control of food density. Finally, the endogenous opioid system was shown to mediate the relationship between food allocation and activity once wheel running was occurring at a high rate.

VII. REFERENCES

Abramson, L. Y. and Seligman, M. E. P. (1977). Modeling psychopathology in the laboratory: history and rationale. In J. D. Maser and M. E. P. Seligman (Eds.), Psychopathology: Experimental Models (pp. 249-271). San Francisco: Freeman.

Ahrens, R. A., Bishop, C. L. and Berdanier, C. D. (1972). Effect of age and dietary carbohydrate source on the responses of rats to forced exercise. Journal of Nutrition, 102, 241-248.

Ahuja, S. K., Manickavel, V., Amy, R. M. and Russell, J. C. (1987). Age-related qualitative and quantitative changes in the endocrine pancreas of the LA/N-corpulent rat. Diabetes Research, 6, 137-144.

American Psychiatric Association. (1987). Diagnostic and statistical manual of mental disorders (3rd ed. rev.). Washington, DC: Author.

Amir, S. (1982). Involvement of endogenous opioids with forced swimming-induced immobility in mice. Physiology and Behavior, 28, 249-251.

Appenzeller, O., Standefer, J., Appenzeller, J. and Atkinson, R. (1980). Neurology of endurance training 5: endorphins. Neurology, 30, 418-419.

Beumont, P. J. V. (1984). A clinician looks at animal models of anorexia nervosa. In N. W. Bond (Ed.), Animal Models in Psychopathology (pp. 177-210). Australia: Academic Press.

Billington, C. J., Morley, J. E., Levine, A. S., Wright, F. and Seal, U. S. (1985). Naloxone induced suppression of feeding in tigers.

Physiology and Behavior, 34, 641-643.

Bloom, F., Segal, D., Ling, N. and Guillemin, R. (1976). Endorphins: profound behavioral effects in rats suggest new etiological factors in mental illness. Science, 194, 630-632.

Blumberg, H. and Dayton, H. B. (1973). Naloxone and related compounds. In H. W. Kosterlitz, H. O. J. Collier and J. E. Villareal (Eds.), Agonist and Antagonist Actions of Narcotic Analgesic Drugs (pp. 110-119). Baltimore: University Park Press.

Blumberg, H. and Dayton, H. B. (1974). Naloxone, naltrexone and related noroxymorphones. In M. C. Braude, L. S. Harris, E. L. May, J. P. Smith and J. E. Villareal (Eds.), Narcotic Antagonists: Advances in Biochemical Psychopharmacology (Vol.8) (pp. 33-43). New York: Raven Press.

Bolles, R. C. (1967). Theory of Motivation. New York: Harper and Row.

Bolles, R. C. (1968). Anticipatory general activity in thirsty rats. Journal of Comparative and Physiological Psychology, 65(3), 511-513.

Bolles, R. C. and de Lorge, J. (1962). The rat's adjustment to a-diurnal feeding cycles. Journal of Comparative and Physiological Psychology, 55(5), 760-762.

Bolles, R. C. and Moot, S. A. (1973). The rat's anticipation of two meals a day. Journal of Comparative and Physiological Psychology, 83(3), 510-514.

Boulous, Z., Rosenwasser, A. M. and Terman, M. (1980). Feeding schedules and the circadian organization of behavior in the rat. Behavioral Brain Research, 1, 39-65.

Boulous, Z. and Terman, M. (1980). Food availability and daily biological rhythms. Neuroscience and Biobehavioral Review, 4, 119-131.

Brands, B., Thornhill, J. A., Hirst, M. and Gowdey, G. W. (1979). Suppression of food intake and body weight gain by naloxone in rats. Life Sciences, 24, 1773-1778.

Bray, G. A. and York, D. A. (1971). Genetically transmitted obesity in rodents. Physiological Reviews, 51(3), 598-646.

Brobeck, J. R., Wheatland, M. and Strominger, J. (1947). Variations in regulation of energy exchange association with estrous, diestrous and pseudo-pregnancy in rats. Endocrinology, 40, 65-77.

Brown, D. R. and Holtzman, S. G. (1979). Suppression of deprivation-induced food and water intake in rats and mice by naloxone. Pharmacology, Biochemistry and Behavior, 11, 567-573.

Bruch, H. (1966). Anorexia nervosa - its differential diagnosis. Journal of Mental and Nervous Disease, 141, 555-566.

Bruning, J. L. and Kintz, B. L. (1977). Computational Handbook of Statistics (2nd ed.). Glenview, Illinois: Scott, Foresman and Company.

Campbell, B. A. (1964). Theory and research on the effects of water deprivation on random activity in the rat. In M. J. Wayner (Ed.), Thirst. Proceedings from the first international symposium on thirst in the regulationof body water (pp. 317-334). Oxford: Pergamon Press.

Campbell, B. A. and Lynch, G. (1967). Activity and thermoregulation during food deprivation in the rat. Physiology and Behavior, 2, 311-313.

Campbell, B. A. and Lynch, G. (1968). Influence of hunger and thirst on the relationship between spontaneous activity and body temperature. Journal of Comparative and Physiological Psychology, 65, 492-298.

Campbell, B. A. and Sheffield, F. D. (1953). Relation of random activity to food deprivation. Journal of Comparative and Physiological Psychology, 46, 320-322.

Campbell, B. A., Teghtsoonian, R. and Williams, R. A. (1961). Activity, weight loss, and survival time of food-deprived rats as a function of age. Journal of Comparative and Physiological Psychology, 54(2), 216-219.

Casper, R. C. (1986). The pathophysiology of anorexia nervosa and bulimia nervosa. Annual Review of Nutrition, 6, 299-316.

Charnov, E. L. (1976). Optimal foraging: the marginal value theorem. Theoretical Population Biology, 9, 129-136.

Cohen, M. R., Cohen, R. M., Pickar, D. and Murphy, D. L. (1985). Naloxone reduces food intake in humans. Psychosomatic Medicine, 47(2), 132-138.

Coleman, G. J., Harper, S., Clarke, J. D. and Armstrong, S. (1982). Evidence for a separate meal-associated oscillator in the rat. Physiology and Behavior, 29, 107-115.

Collier, G. (1969). Body weight loss as a measure of motivation in hunger and thirst. Annals of the New York Academy of Sciences, 157, 594-609.

Collier, G. H. and Rovee-Collier, C. K. (1981). A comparative analysis of optimal foraging behavior: laboratory simulations. In A. C.

Kamil and T. D. Sargent (Eds.), Foraging Behavior: Ecological, Ethological, and Psychological Approaches (pp. 39-76). New York: Garland Press.

Cornish, E. R. and Mrosovsky, N. (1965). Activity during food deprivation and satiation of six species of rodent. Animal Behavior, 13, 242-248.

Cox, B. M. and Baizman, E. R. (1982). Physiological functions of endorphins. In J. B. Malick and R. M. S. Bell (Eds.), Endorphins, Chemistry, Physiology, Pharmacology and Clinical Relevance (pp. 113-196). New York: Marcel Dekker, Inc.

Cumming, D. C., Vickovic, M. M., Wall, S. R. and Fluker, M. R. (1985). Defects in pulsatile LH release in normally menstruating runners. Journal of Clinical Endocrinology and Metabolism, 60(4), 810-812.

Davis, J. M., Lamb, D. R., Lowy, M. T., Yim, G. K. W. and Malven, P. V. (1985). Opioid modulation of feeding behavior following forced swimming exercise in male rats. Pharmacology, Biochemistry and Behavior, 23, 701-707.

Davis, J. M., Lowy, M. T., Yim G. K. W., Lamb, D. R. and Malven, P. V. (1983). Relationship between plasma concentrations of immunoreactive beta-endorphin and food intake in rats. Peptides, 4, 79-83.

DeVore, I. and Hall, K. R. L. (1965). Baboon ecology. In I. DeVore (Ed.), Primate Behavior: Field Studies of Monkeys and Apes (pp. 20-40). New York: Holt, Rinehart and Winston.

Dingledine, R., Iverson, L. L. and Breuker, E. (1978). Naloxone as a

GABA antagonist: evidence from iontophoretic, receptor binding and convulsant studies. European Journal of Pharmacology, 47, 19-27.

Duda, J. J. and Bolles, R. C. (1963). Effects of prior deprivation, current deprivation, and weight loss on the activity of the hungry rat. Journal of Comparative and Physiological Psychology, 56, 569-571.

Epling, W. F. and Pierce, W. D. (1984). Activity-based anorexia in rats as a function of opportunity to run on an activity wheel. Nutrition and Behavior, 2, 37-49.

Epling, W. F. and Pierce, W. D. (1988). Activity-based anorexia: a biobehavioral perspective. International Journal of Eating Disorders, 7(4), 475-485.

Epling, W. F., Pierce, W. D., Russell, J. C., Amy, R. M. and Boer, D. P. (1986, May). Activity-based anorexia: food titration and running level. Paper presented at the meetings of the Association for Behavior Analysis, Milwaukee, Wisconsin.

Epling, W. F., Pierce, W. D. and Stefan, L. (1981). Schedule induced self starvation. In C. M. Bradshaw, E. Szabadi and C. F. Lowe (Eds.), Quantification of Steady-State Operant Behavior (pp. 393-396). Elsevier: North-Holland Biomedical Press.

Epling, W. F., Pierce, W. D. and Stefan, L. (1983). A theory of activity-based anorexia. International Journal of Eating Disorders, 3, 27-46.

Falk, J. L. (1966). Schedule-induced polydipsia as a function of fixed interval length. Journal of the Experimental Analysis of Behavior, 9, 37-39.

Falk, J. L. (1971). The nature and determinants of adjunctive behavior. Physiology and Behavior, 6, 577-588.

Falk, J. L. (1977). The origins and functions of adjunctive behavior. Animal Learning and Behavior, 5(4), 325-335.

Farrell, P. A. (1985). Exercise and endorphins - male responses. Medicine and Science in Sports and Exercise, 17(1), 89-93.

Feighner, J. P., Robins, E., Guze, S. B., Woodruff, R. A., Winokur, G. and Munoz, R. (1972). Diagnostic criteria for use in psychiatric research. Archives of General Psychiatry, 26, 57-63.

File, S. E. (1980). Naloxone reduces social and exploratory activity in the rat. Psychopharmacology, 71, 41-44.

Finger, F. W. (1951). The effect of food deprivation and subsequent satiation upon general activity in the rat. Journal of Comparative and Physiological Psychology, 44, 557-564.

Finger, F. W. (1965). Effect of food deprivation on running-wheel activity in naive rats. Psychological Reports, 16, 753-757.

Gillan, M. G. C., Paterson, S. J. and Kosterlitz, H. W. (1978). Further support for the hypothesis of multiple opiate receptors. In J. M. Van Ree and L. Terenius (Eds.), Characteristics and Functions of Opioids (pp. 475-476). Amsterdam: Elsevier/North Holland Biomedical Press.

Giusti, M., Torre, R., Traverso, L., Cavagnaro, P., Attanasio, R. and Giordano, G. (1988). Endogenous opioid blockade and gonadotropin secretion: role of pulsatile luteinizing hormone-releasing hormone administration in anorexia nervosa and weight loss amenorrhea. Fertility and Sterility, 49(5), 797-801.

Goldstein, A. (1984). Opioid peptides: function and significance. In J. Hughes, H. O. J. Collier, M. J. Rance and M. B. Tyers (Eds.), Opioids: Past, Present and Future (pp. 127-143). London: Taylor and Francis.

Greenhouse, S. W. and Geisser, S. (1959). On methods in the analysis of profile data. Psychometrika, 24, 95-112.

Hall, J. F. (1956). The relationship between external stimulation, food deprivation, and activity. Journal of Comparative and Physiological Psychology, 49, 339-341.

Hall, J. F. and Hanford, P. V. (1954). Activity as a function of a restricted feeding schedule. Journal of Comparative and Physiological Psychology, 47, 362-363.

Hall, J. F., Smith, K., Schnitzer, S. B. and Hanford, P. V. (1953). Elevation of activity level in the rat following transition from ad libitum to restricted feeding. Journal of Comparative and Physiological Psychology, 46, 429-433.

Hamilton, C. L. (1969). Ingestion of nonnutritive bulk and wheel running in the rat. Journal of Comparative and Physiological Psychology, 69(3), 481-484.

Harlow, H. F. and Suomi, S. J. (1974). Induced depression in monkeys. Behavioral Biology, 12, 273-296.

Henry, L. J., Walker, J. and Margules, D. L. (1985). Opposite effects of opiate agonists on metabolic weight loss in mice. Neuropeptides, 5, 327-330.

Herz, A. and Millan, M. J. (1984). Opioid peptides in the hypothalamic-pituatary axis. In J. Hughes, H. O. J. Collier, M.

J. Rance and M. B. Tyers (Eds.), Opioids: Past, Present and Future (pp. 79-102). London: Taylor and Francis.

Hiller, J. M. (1982). The opiate receptor and its endogenous ligands. In N. S. Shah and A. G. Donald (Eds.), Endorphins and Opiate Antagonists in Psychiatric Research: Clinical Implications (pp. 15-39). New York: Plenum.

Himms-Hagen, J. (1985). Defective brown adipose tissue thermogenesis in obese mice. International Journal of Obesity, 9, Suppl. 2, 17-24.

Hoffman-Goetz, L. and MacDonald, M. A. (1983). Effect of treadmill exercise on food intake and body weight in lean and obese rats. Physiology and Behavior, 31, 343-346.

Honma, K., von Goetz, C. and Aschoff, J. (1983). Effects of restricted daily feeding on freerunning circadian rhythms in rats. Physiology and Behavior, 30, 905-913.

Jacquet, Y. F., Klee, W. A., Rice, K. C., Iijima, I. and Minamikawa, J. (1977). Stereospecific and nonstereospecific effects of (+)- and (-)-morphine: evidence for a new class of receptors? Science, 198, 842-845.

Johnson, D. F., Ackroff, K., Peters, J. and Collier, G. H. (1986). Changes in rats' meal patterns as a function of the caloric density of the diet. Physiology and Behavior, 36, 929-936.

Kamil, A. C. and Yoerg, S. I. (1982). Learning and foraging behavior. In P. P. G. Bateson and P. H. Klopfer (Eds.), Perspectives in Ethology Vol. 5 (pp. 325-364). New York: Plenum Press.

Kanarek, R. B. and Collier, G. H. (1979). Patterns of eating as a function of the cost of the meal. Physiology and Behavior, 23, 141-145.

Kanarek, R. B. and Collier, G. H. (1983). Self-starvation: A problem of overriding the satiety signal? Physiology and Behavior, 30, 307-311.

Katch, V. L., Martin, R. and Martin, J. (1979). Effects of exercise intensity on food consumption in the male rat. The American Journal of Clinical Nutrition, 32, 1401-1407.

Katz, J. L. (1986). Running and anorexia nervosa. Comprehensive Psychiatry, 27(1), 74-78.

Kaye, W. H., Pickar, D. M., Naber, D. and Ebert, M. H. (1982). Cerebrospinal fluid opioid activity in anorexia nervosa. American Journal of Psychiatry, 139(5), 643-645.

King, A. (1963). Primary and secondary anorexia nervosa syndromes. British Journal of Psychiatry, 109, 470-479.

Krebs, J. R. (1978). Optimal foraging: decision rules for predators. In J. R. Krebs and N. B. Davies (Eds.), Behavioural Ecology: an Evolutionary Approach (pp. 23-63). Sunderland, Massachusetts: Sinauer Associates, Inc.

Krebs, J. R., Houston, A. I. and Charnov, E. L. (1981). Some recent developments in optimal foraging. In A. C. Kamil and T. D. Sargent (Eds.), Foraging Behavior: Ecological, Ethological and Physiological Approaches (pp. 3-18). New York: Garland Press.

Kron, L., Katz, J. L., Gorzynski, G. and Weiner, H. (1978). Hyperactivity in anorexia nervosa: a fundamental feature. Comprehensive Psychiatry, 19(5), 433-439.

Lee, T. F., Wang, L. C. H. and Russell, J. C. (1987). Enhancement of cold-stimulated thermogenesis in the corpulent rat (LA/N-cp) by aminophylline. American Journal of Physiology, 252, 737-742.

LeMagnen, J. and Devos, M. (1980). Parameters of the meal pattern in rats: their assessment and physiological significance. Neuroscience and Biobehavioral Reviews, 4, Suppl. 1, 1-11.

Levitsky, D. A. (1970). Feeding patterns of rats in response to fasts and changes in environmental conditions. Physiology and Behavior, 5, 291-300.

Levitsky, D. A. (1974). Feeding conditions and intermeal relationships. Physiology and Behavior, 12, 779-787.

Levitsky, D. and Collier, G. (1968). Schedule-induced wheel running. Physiology and Behavior, 3, 571-573.

Litt, I. F. and Glader, L. (1986). Anorexia nervosa, athletics, and amenorrhea. The Journal of Pediatrics, 109(1), 150-153.

Looy, H. and Eikelboom, R. (1989). Wheel running, food intake, and body weight in male rats. Physiology and Behavior, 45, 403-405.

Lord, J. A. H., Waterfield, A. A., Hughes, J. and Kosterlitz, H. W. (1977). Endogenous opioid peptides: multiple agonists and receptors. Nature, 267, 495-499.

Loy, J. (1970). Behavioral responses of free-ranging rhesus monkeys to food shortage. American Journal of Physical Anthropology, 33, 263-272.

Luby, E. D., Marrazzi, M. A. and Kinzie, J. (1987). Case reports-treatment of chronic anorexia nervosa with opiate blockade. Journal of Clinical Psychopharmacology, 7(1), 52-53.

Mahon, K., DeHaas, B. M. and Eikelboom, R. (1986). The nature of the sex difference in activity induced self-starvation. Canadian

Psychology/Psychologie Canadienne, 27(2a), 374.

Mayer, J. (1953). Decreased activity and energy balance in the hereditary obesity-diabetes syndrome of mice. Science, 117, 504-505.

McFarland, D. J. (1977). Decision making in animals. Nature, 269, 15-21.

McKinney, W. T. and Bunney, W. E. (1969). Animal model of depression. Archives of General Psychiatry, 21, 240-248.

McLaughlin, C. L. and Baile, C. A. (1984a). Feeding behavior responses of Zucker rats to naloxone. Physiology and Behavior, 32, 755-761.

McLaughlin, C. L. and Baile, C. A. (1984b). Increased sensitivity of Zucker obese rats to naloxone is present at weaning. Physiology and Behavior, 32, 929-933.

McMillan, D. E., Wolf, P. S. and Carchman, R. A. (1970). Antagonism of the behavioral effects of morphine and methadone by narcotic antagonists in the pigeon. The Journal of Pharmacology and Experimental Therapeutics, 175(2), 443-458.

Mills, I. H. and Medlicott, L. (1984). The basis of naloxone treatment in anorexia nervosa and the metabolic responses to it. In K. M. Pirke and D. Ploog (Eds.), The Psychobiology of Anorexia Nervosa (pp. 161-171). Berlin: Springer-Verlag.

Moskowitz, M. J. (1959). Running-wheel activity in the white rat as a function of combined food and water deprivation. Journal of Comparative and Physiological Psychology, 56(3), 569-571.

Mrosovsky, N. and Sherry, D. F. (1980). Animal anorexias. Science, 207, 837-842.

Pang, C. N., Zimmerman, E. and Sawyer, C. H. (1977). Morphine inhibition of preovulatory surges of plasma LH and FSH in the rat. Endocrinology, 101, 1726-1732.

Peng, M. T. and Kang, M. (1984). Circadian rhythms and patterns of running-wheel activity, feeding and drinking behaviors of old male rats. Physiology and Behavior, 33, 615-620.

Pierce, W. D., Epling, W. F. and Boer, D. P. (1986). Deprivation and satiation: The interrelations between food and wheel running. Journal of the Experimental Analysis of Behavior, 46, 199-210.

Pinsky, C., LaBella, F. S., Havlicek, V. and Dua, A. K. (1978). Apparent agonist actions of naloxone in the unrestrained rat. In J. M. Van Ree and L. Terenius (Eds.), Characteristics and Functions of Opioids (pp. 439-440). Amsterdam: Elsevier/North-Holland Biomedical Press.

Prins, A. A., de Jong-Nagelsmit, A., Keijser, J. and Strubbe, J. H. (1986). Daily rhythms of feeding in the genetically obese and lean zucker rats. Physiology and Behavior, 38, 423-426.

Reid, L. D. (1985). Endogenous opioid peptides and regulation of drinking and feeding. The American Journal of Clinical Nutrition, 42, 1099-1132.

Reid, L. S. and Finger, F. W. (1955). The rat's adjustment to 23-hour food-deprivation cycles. Journal of Comparative and Physiological Psychology, 48, 110-113.

Richter, C. P. (1922). A behavioristic study of the activity of the rat. Comparative Psychological Monographs, 1(2), 1-55.

Richter, C. P. (1927). Animal behavior and internal drives. Quarterly

Review of Biology, 2, 307-343.

Risch, S. C., Janowsky, D. S., Judd, L. L., Gillin, J. C. and McClure, S. F. (1983). The role of endogenous opioid systems in neuroendocrine regulation. Psychiatric Clinics of North America, 6(3), 429-441.

Ropert, J. F., Quigley, M. E. and Yen, S. S. C. (1981). Endogenous opiates modulate pulsatile luteinizing hormone release in humans. Journal of Clinical Endocrinology and Metabolism, 52(3), 583-585.

Rosenwasser, A. M., Pelchat, R. J. and Adler, N. T. (1984). Memory for feeding time: possible dependence on coupled circadian oscillators. Physiology and Behavior, 32, 25-30.

Routtenberg, A. (1968). "Self-starvation" of rats living in activity wheels: adaptation effects. Journal of Comparative and Physiological Psychology, 66(1), 234-238.

Routtenberg, A. and Kuznesof, A. W. (1967). "Self-starvation" of rats living in activity wheels on a restricted feeding schedule. Journal of Comparative and Physiological Psychology, 64, 414-421.

Russell, J. C. and Amy, R. M. (1986a). Early atherosclerotic lesions in a susceptible rat model: the LA/N-corpulent rat. Atherosclerosis, 60, 119-129.

Russell, J. C. and Amy R. M. (1986b). Myocardial and vascular lesions in the LA/N-corpulent rat. Canadian Journal of Physiology and Pharmacology, 64, 1272-1280.

Russell, J. C., Epling, W. F., Pierce, W. D., Amy, R. M. and Boer, D. P. (1987). Induction of prolonged running by rats. Journal of

Applied Physiology, 63(6), 2549-2553.

Russell, J. C., Amy, R. M., Manickavel, V., Dolphin, P. J., Epling, W. F., Pierce, W. D. and Boer, D. P. (1989). Prevention of myocardial disease in JCR:LA-corpulent rats by running. Journal of Applied Physiology, 66(4), 1649-1655.

Sanger, D. J. and McCarthy, P. S. (1980). Differential effects on morphine on food and water intake in food deprived and freely-feeding rats. Psychopharmacology, 72, 103-106.

Sawynok, J., Pinsky, C. and LaBella, F. S. (1979). Minireview on the specificity of naloxone as an opiate antagonist. Life Sciences, 25(19), 1621-1632.

Schnur, P. (1985). Effects of naloxone and naltrexone on morphine-elicited changes in hamster locomotor activity. Physiological Psychology, 13(1), 26-32.

Schnur, P. and Hang, D. (1987). Naloxone reversal of morphine elicited hyperactivity. Life Sciences, 40, 329-333.

Schnur, P. and Raigoza, V. P. (1986). Effects of naloxone on morphine induced sedation and hyperactivity in the hamster. Pharmacology, Biochemistry and Behavior, 24, 849-854.

Seaver, R. L. and Binder, H. J. (1972). Anorexia nervosa and other anorectic states in man. Advances in Psychosomatic Medicine, 7, 257-276.

Seevers, M. H. and Deneau, G. A. (1962). A critique of the "dual action" hypothesis of morphine physical dependence. Archives Internationales de Pharmacodynamie et de Therapie, 140, 514-520.

Shido, O., Nagasaka, T. and Noda, Y. (1986). Effects of chronic administration of naloxone on wheel running activity in rats under 2-h feeding schedule. Japanese Journal of Physiology, 36, 555-564.

Stevenson, J. A. F., Box, B. M., Feleki, V. and Beaton, J. R. (1966). Bouts of exercise and food intake in the rat. Journal of Applied Physiology, 21(1), 118-122.

Stevenson, J. A. F. and Rixon, R. H. (1957). Environmental temperature and deprivation of food and water on the spontaneous activity of rats. Yale Journal of Biology and Medicine, 29, 575-584.

Suomi, S. J. (1982). Relevance of animal models for clinical psychology. In Handbook of Research Methods in Clinical Psychology (pp. 249-271). New York: John Wiley and Sons, Inc.

Tepperman, F. S., Hirst, M. and Smith, P. (1983). Brain and serum levels of naloxone following peripheral administration. Life Sciences, 33, 1091-1096.

Thompson, D. A. and Campbell, R. G. (1977). Hunger in humans induced by 2-deoxy-D-glucose: glucoprivic control of taste preference and food intake. Science, 198, 1065-1068.

Tokuyama, K., Saito, M. and Okuda, H. (1982). Effects of wheel running on food intake and weight gain of male and female rats. Physiology and Behavior, 28, 899-903.

Treichler, F. R. and Hall, J. F. (1962). The relationship between deprivation weight loss and several measures of activity. Journal of Comparative and Physiological Psychology, 55(3), 346-349.

Tulp, O. L. (1984). Impaired activation of thermogenesis in the corpulent rat. Life Sciences, 35, 1699-1704.

Vasko, M. R. and Domino, E. F. (1978). Tolerance development to the biphasic effects of morphine on locomotor activity and brain acetylcholine in the rat. The Journal of Pharmacology and Experimental Therapeutics, 207(3), 848-858.

Vaughan, W. and Herrnstein, R. J. (1987). Choosing among natural stimuli. Journal of the Experimental Analysis of Behavior, 47, 5-16.

Walker, J. M., Berntson, G. G., Paulucci, T. S. and Champney, T. C. (1981). Blockade of endogenous opiates reduces activity in the rat. Pharmacology, Biochemistry and Behavior, 14, 113-116.

Warren, M. P. (1983). Effects of undernutrition on reproductive function i the human. Endocrine Reviews, 4(4), 363-377.

Weasner, M. H., Finger, F. W. and Reid, L. S. (1960). Activity changes under food deprivation as a function of recording device. Journal of Comparative and Physiological Psychology, 53(5), 470-474.

Woods, D. J. and Routtenberg, A. (1971). "Self-starvation" in activity wheels: developmental and chlorpromazine interactions. Journal of Comparative and Physiological Psychology, 76(1), 84-93.

Wright, J. H., Gescheider, G. A. and Johnson, M. L. (1966). Energizing effects of combined food and water deprivation upon general activity. Psychonomic Science, 5, 415-416.

Yen, T. T. T. and Acton, J. M. (1972). Locomotor activity of various types of genetically obese mice. Proceeding of the Society for Experimental Biology and Medicine, 140, 647-650.

Zielinski, W. J. (1986). Circadian rhythms of small carnivores and the effect of restricted feeding on daily activity. Physiology and Behavior, 38, 613-620.

VIII. APPENDIX A: LITERATURE REVIEW

The biobehavioral perspective of "activity-anorexia" (Epling and Pierce, 1988) suggests that food deprivation and meal schedule interrelate with physical activity in the production of certain instances of self-starvation. From this perspective, physical activity reduces the value of food reinforcement and results in decreased food intake. Lower food intake concomittant with a decline in body weight, increases the motivational value of exercise, further reducing the reinforcing value of food. Thus, food intake and body weight interact to produce excessive running in activity-anorexia.

Pierce, Epling and Boer (1986) report behavioral data which showed that the reinforcing efficacy of wheel running increases with increasing food deprivation. Epling and Pierce (1988) suggested that the relationship between exercise and eating may be mediated by the endogenous opioid system. Research evidence supports endogenous opioid mediation of the effects of activity on eating (e.g., Davis, Lamb, Lowy, Yim and Malven, 1985), and the present data (experiment four) offers evidence of endogenous opioid mediation of the effects of food deprivation upon anorexic activity. The purpose of the present review is to examine the behavioral, evolutionary and physiological bases of activity-anorexia. The final section of this literature review evaluates activity-anorexia as an animal model of psychopathology.

A. Behavioral Basis of Activity-Anorexia

1. Food deprivation affects activity

Certain species of animals substantially increase activity as measured by wheel running when food deprived (e.g., Campbell and Sheffield, 1953; Cornish and Mrosovsky, 1965; Finger, 1951, 1965; Hall, 1956; Hall and Hanford, 1954; Hall, Smith, Schnitzer and Hanford, 1953; Routtenberg and Kuznesof, 1967; Routtenberg, 1968; Treichler and Hall, 1962; Woods and Routtenberg, 1971; Zielinski, 1986). For example, Hall and Hanford (1954) found that rats on 23h food deprivation showed a marked increase in daily running activity compared to control animals on free food. In another experiment, Finger (1951) using rats investigated the effects of two levels of food deprivation (24 and 72h) upon activity. He found that amount of wheel running increased markedly with deprivation level. Finger (1965) later replicated this effect using three levels of food deprivation (0, 24 and 48 hours).

Cornish and Mrosovsky (1965) extended the generality of the effects of food deprivation upon activity using six species of rodents. It was found that after 3 days of food deprivation rats and guinea pigs (non-hibernators) increased wheel running; whereas dormice, ground squirrels and chipmunks (hibernators) showed no change or a decrease (chipmunks only) in running activity. The only exception was the hamster (a hibernator) which increased activity with deprivation perhaps because of its reliance on hoarded supplies of food during the winter.

Weasner, Finger and Reid (1960) found that rats on 23h food deprivation housed in stationary cages doubled daily activity. Reid and Finger (1955) found that similarly deprived rats housed in activity wheels increased running by a factor of ten or more. Similarly, Treichler and Hall (1962) examined activity levels of food and water deprived rats housed either in activity wheels, stabilimeter cages or Dashiell mazes. Wheel running increased markedly with continuous deprivation, but maze and stabilimeter measures showed little change. Interestingly, no differences in weight loss were found during the first 4 days of deprivation for all rats, but rats housed in activity wheels died at a body weight higher than maintenance weights for rats housed in stabilimeters. Similarly, Campbell and Sheffield (1953) found that 7 days of continuous food deprivation produced a "relatively small increase in activity (p. 321)" for rats in stabilimeter cages. Campbell (1964) using rats examined separately the effects of water and food deprivation upon activity in stabilimeter cages and running wheels. He found no significant increase in activity with water deprivation, but "sizeable" increases by food deprived animals using stabilimeter cages. By contrast, both water and food deprived rats showed rapid and significant increments in wheel running. Campbell (1964) noted that survival time during deprivation is much longer for rats housed in stabilimeter cages than for rats housed in activity wheels. Taken together, the studies by Weasner, Finger and Reid (1960), Treichler and Hall (1962) and Campbell (1964) suggest that wheel running is a unique behavioral response to food deprivation. This is in contrast to random cage activity which does not increase by the same magnitude as wheel running during food deprivation. Increased running activity during periods of food scarcity may have survival value and is examined in a later section of this review.

Finally, some studies have analyzed the effects of combined food and water deprivation upon activity. For example, Wright, Gescheider and Johnson (1966) using rats looked at the effects of 72h continuous food and water deprivation upon wheel running. It was found that activity increased as a function of deprivation for these stimuli.

In conclusion, studies have shown that certain species of rodents will significantly increase activity, particularly wheel running, when deprived for food, water, or both.

2. Activity as a function of body weight loss

The increase in wheel running activity observed with food deprivation has been attributed to a decrease in body weight (e.g., Bolles, 1967; Collier, 1969; Duda and Bolles, 1963; Moskowitz, 1959; Treichler and Hall, 1962). For example, Collier (1969) reported a study which compared wheel running in two groups of rats, one water deprived and the other food deprived. His results indicated that wheel turning with water and food deprivation was a linear log log function of percentage weight loss. Similarly in one study, Moskowitz (1959) allowed rats wheel access 1h/day and found that wheel running was a function of weight loss after weight decreased to 85-90% ad libitum weight.

In another study, Duda and Bolles (1963) exposed 7 groups of rats to different food deprivation conditions and determined that the main effect of the deprivation conditions was differential weight loss. The deprivation conditions included 24, 48, 72 and 96h continuous food deprivation prior to a 24h test period in an activity wheel (also without food). In addition, three other groups of rats were given exposure to 0, 24 or 48h food deprivation after 10 days of a 1h/day feeding schedule prior to the 24h activity test period. These authors found that the number of wheel turns made in the post-deprivation 24h period was related to body weight loss independent of number of hours of food deprivation. Taken together, these studies suggest that running wheel activity is a function of body weight loss for food deprived animals.

3. Activity affects food consumption

Routtenberg and Kuznesof (1967) noted that several studies (e.g., Hall and Hanford, 1954; Weasner, Finger and Reid, 1960) reported that food deprived rats exposed to single daily meals of 2h duration or less failed to maintain stable body weight and some subjects died. Routtenberg and Kuznesof (1967) extended these findings in an examination of "self-starvation" of rats housed in activity wheels and maintained on various schedules of food deprivation. In one study, these authors found that rats which were food deprived for 23h and allowed free access to an activity wheel "self-starved" and died. That is, these animals revealed a marked decrease in food intake compared to control subjects. Concomittant with this decrease in food intake was a significant increase in amount of wheel running over days. Control subjects on the same food deprivation schedule without a running wheel stabilized body weight and survived.

Similarly, Epling, Pierce and Stefan (1981, 1983) showed that when food is restricted to one meal/day wheel running increases. Such a feeding schedule generally results in lower food intake and a concomittant decrease in body weight. Epling, Pierce and Stefan (1983) found that as body weight decreases wheel running increases and that this increase in activity results in a further decline in food intake.

Other studies have also shown that exercise reduces food intake in rats (e.g., Ahrens, Bishop and Berdanier, 1972; Hoffman-Goetz and

MacDonald, 1983; Katch, Martin and Martin, 1979; Levitsky, 1970; and Stevenson, Box, Feleki and Beaton, 1966). For example, Levitsky (1970) found that running wheel access significantly decreases food intake as measured by the number of meals consumed per day. Similarly, Katch, Martin and Martin (1979) showed that forced treadmill exercise of a high intensity (16m/min, 10% incline) decreased food intake and weight gain compared to low intensity (5m/min, 0% incline) exercise in rats. Both exercised groups had lower food intake and weight gain compared to non-exercised controls.

Stevenson, Box, Feleki and Beaton (1966) found that forced treadmill running of 1080 m/day or swimming (1 or 2h/day) reduced food intake in free-feeding rats on the day the exercise was forced. Reduction in food intake was even greater in rats on a 3h/day feeding schedule and exposed to similar forced exercise. Interestingly, the forced exercise rats and controls were housed in activity wheels and controls made more "spontaneous" wheel turns/day than the exercised rats. It is possible that forced exercise may alter the reinforcing effectiveness of spontaneous running - if these activities are different. In this regard, Pierce, Epling and Boer (1986) found that satiation for wheel running, by spontaneous or forced wheel running, decreased the reinforcing effectiveness of food. Thus, the reinforcing efficacy of voluntary or forced wheel running may be affected similarly by food deprivation but still be quantitatively differentiable with respect to each other.

The review and results of Russell, Epling, Pierce, Amy and Boer (1987) suggest that forced and voluntary (spontaneous) running may be quantitatively different. This is because rats will not run significant distances voluntarily on treadmills or motorized wheels, but will run 8 km/day in a free wheel when mildly food-deprived (15-18g/day). Thus, voluntary and forced running appear quantitatively different.

Several studies have noted that this reduction in food intake recovers if activity does not become excessive (e.g., Levitsky, 1970; Looy and Eikelboom, 1989; Tokuyama, Saito and Okuda, 1982). For example, Levitsky (1970) found that rats with activity wheels given ad libitum food gradually increased amount eaten per meal but continued to consume fewer meals per day than inactive animals. However, total food intake did not differ by the end of the experimental phase (17 days). Thus, rats increased food intake by consuming larger meals. This finding is similar to results of a study by Kanarek and Collier (1979). These authors made rats complete an ascending series of fixed ratio (FR) schedules of wheel turns (20, 40, 80, 160, 320, 640, 1280 and 2560) for food access. Each schedule value was in effect for 12 days. As the ratio requirement increased meal frequency decreased and amount eaten per meal increased. The increased amount eaten was primarily due to an increase in meal duration (e.g., 40 min/meal at FR 1280) as the rats ate at a constant rate throughout the experiment (0.4-0.5 g/min). However, at FR 2560 meal duration decreased to about 10 min and food intake per meal was only 3 to 5g. Thus, an increased requirement in activity resulted in decreased food intake and weight loss.

In another study, Tokuyama, Saito and Okuda (1982) gave free access to a running wheel to 50 day old male and female rats on ad libitum food. Running activity of female rats increased "rapidly" over the first 10 days of the experiment to a stable level of about 11000 revs/day. During the first 5 days of this period, food intake of the exercising female rats was lower than that of sedentary controls, but after this period the exercising rats ate more than the controls. Running activity of the male rats in this study running also plateaued after 10 days but at 4000 revs/day. As with the female rats, the first 10 days food intake was lower for the exercising male rats than for sedentary controls, then increased. The apparent sex difference in activity in this study is probably due to the initial weight difference between male and female rats. Although the rats were matched for weight and age ten days prior to the experiment, the male rats were almost 100g heavier than the female rats on day 1 and this weight difference increased over the course of the study. This analysis gains support from Mahon, DeHaas and Eikelboom (1986). These researchers determined that apparent sex differences in number of days to a 30% weight loss criterion (for rats exposed to a 23h food deprivation schedule with activity wheel access) were due to initial weight differences.

In summary, free-feeding rats given wheel access are able to compensate for an increase in activity by increasing food intake over days, whereas food restricted rats continue to increase activity and "self-starve" (Epling and Pierce, 1984). Other studies show that forced exercise (e.g., Stevenson, Box, Feleki and Beaton, 1966) or the opportunity to exercise (e.g., Tokuyama, Saito and Okuda, 1982) reduces food consumption in free-feeding rats. Finally, the opportunity to run (e.g., Levitsky, 1970) or the requirement to run to obtain food (e.g., Kanarek and Collier, 1979) results in a decrease in meal frequency and an increase in meal size. However, this relationship changes when the running level becomes excessive, at which point food intake is decreased.

4. Food allocation affects activity

As noted earlier, food deprivation increases activity in rodents (e.g., Routtenberg and Kuznesof, 1967). However, this increase in activity is not distributed evenly throughout a 24h period. Rather, a significant portion is coupled to the time of feeding and is termed "anticipatory activity" (e.g., Boulous, Rosenwasser and Terman, 1980; Boulous and Terman, 1980; Honma, von Goetz and Aschoff, 1983; Peng and Kang, 1984; Richter, 1922, 1927; Reid and Finger, 1955; Rosenwasser, Pelchat and Adler, 1984; and Zielinski, 1986).

A study by Zielinski (1986) found anticipatory activity in food restricted weasels and minks in a 12/12h light-dark cycle with constant illumination using running wheels and tilt cages. Similar activity was not exhibited by weasels and minks on ad libitum food. This latter finding is in accord with Hall and Hanford (1954) who found that rats on ad libitum food exhibited constant running levels. In addition, Reid and Finger (1955) found that rats on 23h food deprivation increased activity in the hour prior to feeding over the duration of their experiment (35 days).

Richter (1922) exposed rats to a restricted feeding schedule of 25-min/day at noon each day and measured activity in a primitive stabilimeter cage. He found that following the feeding period there was a period of "relative" inactivity for 4 to 5 hours, followed by 8 to 10 hours of increased activity, then 5 to 7 hours of "complete" inactivity, and a rapid and sustained increase in activity in the 2 to 3 hours prior to feeding. Importantly, Richter found this behavioral periodicity using constant illumination suggesting that a light-dark cycle is not necessary for the occurrence of anticipatory activity. In addition, Bolles (1968) found anticipatory running in 23.5h water-deprived rats. This anticipatory increase was found even when there was no overall increase in wheel running. Finally, Bolles and de Lorge (1962) found anticipatory activity in rats on 24h feeding cycles but not on feeding cycles less than 19h or greater than 29h. Thus, Bolles and de Lorge (1962) claimed that anticipatory activity is circadian in nature, i.e., it has 24h periodicity.

Honma, von Goetz and Aschoff (1983) replicated and extended the findings of Richter (1922). These authors exposed rats to either 2 or 4h/day food schedules and found the same activity patterns as Richter (1922). Interestingly, they also found that rats on the different feeding schedules exhibited similar amounts of anticipatory activity. In addition, Bolles and Moot (1973) showed that rats fed 1h meals twice daily exhibited anticipatory activity before each meal. Thus, the total amount of anticipatory activity increased with meal frequency.

A study by Kanarek and Collier (1983) showed that the imposition of one 60-min, two 30-min, or four 15-min feeding schedules affected wheel running activity. As meal frequency increased, total food intake increased, and the level of total wheel turns/day decreased. Unfortunately, these authors did not examine anticipatory activity on the different feeding schedules. However, given the results of Bolles and Moot (1973) it is possible that the four 15-min meal schedule produced more anticipatory activity (although this schedule produced less activity overall) than the one 60-min or two 30-min schedules. Taken together, these studies (Bolles and Moot, 1973; Honma, von Goetz and Aschoff, 1983; Richter, 1922; Kanarek and Collier, 1983) suggest that restricted feeding schedules result in anticipatory activity, but the level of anticipatory activity does not increase with the extent of food deprivation, but rather with meal frequency. Thus, the excessive activity observed in activity-anorexia is not due to an increase in anticipatory activity alone. Conversely, the additional feeding opportunities may disrupt the circadian running which is not anticipatory in nature (i.e., the 8 to 10 hours of activity which follows the initial inactive period found by Richter, 1922).

In another study, Hamilton (1969) showed that rats starved for a 5 day period and given ad libitum nonnutritive edible bulk during this period were much less active than starved rats not receiving the bulk. Importantly, both groups of rats lost weight at the same rate. Thus, the activity difference is not due to differential weight loss.

In summary, the above studies show that level and pattern of activity are related to food allocation. That is, the allocation of food by regular discrete meals results in an increase in amount of daily activity plus the patterning of activity into "active" and "inactive" periods (e.g., Richter, 1922; Honma, von Goetz and Aschoff, 1983). However, an increase in meal frequency causes a decrease in activity (Kanarek and Collier, 1983) but not in anticipatory activity (Bolles and Moot, 1973). Finally, Hamilton (1969) showed that feeding decreases activity levels even if the food is nonnutritive.

5. Summary

Food restriction and running-wheel availability have been shown to be sufficient conditions for producing excessive locomotor activity in rats (e.g., Routtenberg and Kuznesof, 1967). Epling and Pierce (1984) reported that rats exposed to free wheel and food restriction initially increased food intake and made a moderate amount of wheel turns. After a few days, as activity increased food intake levelled off, and as activity subsequently peaked food intake markedly declined. During this time, body weight decreased as a function of food intake, which was a function of rate of change in daily activity. Epling and Pierce (1984) concluded that "body weight decline was due to the indirect effects of activity on food intake and the direct effects of rate of wheel running on energy expenditure (p. 37)". Thus, the initial activity observed during activity-anorexia may begin as a function of percentage body weight loss (e.g., Collier, 1969) which is a function of food intake (Epling and Pierce, 1984).

In addition, studies have shown that if provided the opportunity to exercise or if exercise is forced, food intake is decreased in food restricted rats (e.g., Epling and Pierce, 1984) and in free-feeding rats (e.g., Stevenson, Box, Feleki and Beaton, 1966). Importantly, free-feeding rats increase food intake over days (e.g., Tokuyama, Saito and Okuda, 1982) whereas food restricted rats continue to increase activity and "self-starve" (Epling and Pierce, 1984). These studies support the claim that rate of change in activity is critical to suppression of food intake (Epling and Pierce, 1984). Finally, studies have shown that amount and pattern of activity are related to food allocation (e.g., Hamilton, 1969; Kanarek and Collier, 1983; Richter, 1922).

In summary, evidence supports the claim that body weight loss and food allocation interact in the generation of excessive activity in activity-anorexia (Epling and Pierce, 1988). The present research showed that running initially increases as body weight declines. However, once established, high activity levels become sensitive to changes in food allocation not changes in body weight.

B. Evolutionary Basis of Activity-Anorexia

1. Survival value of increased activity during food scarcity

Epling and Pierce (1988) have proposed that activity-anorexia "may be the result of natural selection favoring those organisms that became active in times of food scarcity" (p. 475). There are many laboratory studies which show that deprivation for food increases activity in various species of rodents (e.g., Cornish and Mrosovsky, 1965). Similarly, the optimal foraging literature suggests that animals should increase locomotor activity (i.e., travelling between food patches) when food supplies are diminished within a patch (e.g., Charnov, 1976; Krebs, 1978).

In brief, the marginal value theory (an optimal foraging model) (Charnov, 1976) describes foraging behavior in a "patchy" environment. According to this model, food is found only within patches. The animal must spend time travelling between patches (time without food), or searching for, identifying, procuring, handling and consuming food within a patch (Collier and Rovee-Collier, 1981). The longer an animal stays in a particular patch, the more food items are consumed and the benefit of staying in that patch diminishes (Charnov, 1976). Charnov (1976) states that the animal "should leave the patch it is presently in when marginal capture rate in the patch (the marginal value) . . . drops to the average capture rate for the habitat" (p. 132). That is, if an animal is to maximize its net energy gain from foraging in a particular food patch, it should leave the patch when its expected net gain from staying in the present patch decreases to the level of the expected net gain from traveling to and searching in the next food patch (Charnov, 1976). Krebs (1978) summarizes the marginal value theory by stating "(an animal) should not stay in patch when it could do better by travelling to another one" (p. 43).

Krebs, Houston and Charnov (1981) cite several studies which show that the marginal value model of optimal foraging predicts the observed relationship "between travel time and time in a patch, especially when the energy cost of travelling between patches is incorporated" (p. 8). Other studies have also shown that food shortage within a feeding area results in an increase in foraging (e.g., Loy, 1970). For example, DeVore and Hall (1965) found that the most important factor affecting distance travelled per day for baboons in Africa was the amount of available food. Sparse vegetation resulted in travel of up to 12 miles/day, whereas a rich food source (e.g., a fig tree) resulted in only a few yards of travel on a particular day (DeVore and Hall, 1965).

Recent developments in optimal foraging models have gone beyond the description of foraging behavior to formulations of how animals behave in terms of expected rates of food intake. According to Krebs, Houston and Charnov (1981), optimal foragers are assumed to compare an expectation of their "current gain rate with an expectation derived from past experience, and the expectation should change according to average conditions in the environment" (p. 11). How animals come to have these expectations and how they compare them to each other is seen as the focus of optimal foraging theory. For example, McFarland (1977) states "the animal can be seen as carrying out a cost-benefit analysis in making its decisions. If the animal is not closely adapted to its environment, it may not make the analysis correctly" (p. 20).

In summary, optimal foraging theory describes the behavior of animals foraging in a patchy environment (e.g., Krebs, Houston and Charnov, 1981). However, the theory has been extended to the study of speculative mental processes underlying optimal foraging behavior and not further analysis of the behavior per se.

2. Food consumption by rats occurs in meals

An early study by Richter (1927) showed that food consumption by rats occurs in discrete episodes or meals. He found that rats given ad libitum food fed every three hours on average and consumed 7-10 meals per day. Richter (1927) observed that this feeding rhythm obtained a constant average over days for each rat.

The periodicity of food intake by rats was examined further by LeMagnen and Devos (1980). Similar to Richter (1927), these authors found that rats eat discrete meals separated by intervals of differing durations. The short-term periodicity or between meal interval, is called the "prandial" periodicity. Superimposed on prandial periodicity, is a "diurnal" periodicity, or 24hr light-dark periodicity. For example, rats eat larger, more frequent meals during the active (dark) phase of a 12:12 light-dark cycle, and smaller, less frequent meals in the inactive (light) phase.

There is a great deal of variation in the experimental definition of a meal. Richter (1927) defined meal initiation as the rat reaching for the food cup which was placed at the end of a tunnel. Contacting the food cup resulted in a kymograph recording of eating whether the rat had eaten or not. Levitsky (1970) chose a feeder photocell beam interruption of 30 sec or more as the criterion for meal initiation. Meal duration was measured from this point until a period of at least 10 min of non-eating occurred at which time the meal was considered terminated. In another study, Levitsky (1974) redefined a meal as being a "(feeding) tunnel entrance during which no less than 0.1g food was consumed and where at least 15 min of no further tunnel entrances occurred" (p. 781). LeMagnen and Devos (1980) attempted to define a meal less arbitrarily based on rat's free-feeding behavior. These authors found that although rats eat discrete meals, these meals do not consist of uninterrupted bouts of eating, followed and preceded by discrete period of non-eating. LeMagnen and Devos (1980) concluded that the feeding behavior of rats may be described as consisting of pauses or short interruptions within meals and inter-meal intervals. Within meal pauses are less than 40 min and most often 2 to 10 min in duration, while intervals between meals are greater than 40 min in length. Thus a meal was defined in terms of a meal-to-meal interval of at least 40 min of non-feeding. Taken together, these studies show that rats consume discrete meals and that meals can be experimentally defined and measured.

3. Summary

In summary, the foraging literature suggests that an increase in locomotor activity when food supplies within a patch are diminished has survival value (e.g., Krebs, Houston and Charnov, 1981). However, Epling and Pierce (1988) state, "during periods of food scarcity, travel should not stop when food is infrequently contacted, since stopping to eat may be negatively balanced against getting to a richer food patch. Increasing contact with food would indicate a replenished supply, and travel should reduce or stop at this time (p. 480)". Continued high rate activity would ensure that the animals would not stay in a patch if it would benefit by travelling to a new patch. In addition, food consumption by rats occurs in meals (e.g., Richter, 1927) and therefore changes in total food intake must result from alterations in meal size or frequency, or both (Johnson, Ackroff, Peters and Collier, 1986). As reviewed earlier, an increase in meal frequency (e.g., dividing a 1-hr feeding period into four 15-min periods) has been shown to reduce wheel running activity (Kanarek and Collier, 1983). From a foraging perspective, changes in food density should correspond in a reciprocal fashion to changes in the amount of wheel running by food restricted rats (cf., Experiment Three).

C. Physiological Basis of Activity-Anorexia

Pierce, Epling and Boer (1986) showed that there is a reciprocal relationship between the reinforcing efficacy of wheel running and eating. Epling and Pierce (1988) suggested that physiological mechanism(s) mediate the relationship between running and eating. In particular, Epling and Pierce (1988) proposed that the endogenous opioid system links the motivational value of running and eating in activity-anorexia once high activity levels are established.

1. Stomach contractions and thermogenesis

Richter (1927) inferred from his data that "periods of gross bodily activity in the rat are associated with periods of gastric movement which have to do with the hunger responses of the animal" (p. 311). He found that there was a correlation between cage activity, feeding and stomach contractions. In fact, small stomach contractions occurred simultaneously with the beginning of an active period and as the stomach contractions became stronger the animal became more active. Richter (1927) concluded that the "two-hour activity rhythm in the rat is dependent on gastric function" (p. 316). In support of Richter's (1927) study, Hamilton (1969) reported data which showed that rats receiving non-nutritive bulk ran less than rats receiving no food bulk at all. Hamilton (1969) argued that the initial increase in wheel running during starvation was due to the emptiness of the gut. However, data from the present study (experiment two) contradicts Hamiton's (1969) claim as rats receiving food ran more than starved rats. Since stomach contractions occur when the gut is empty, the increased activity of the 90min meal rats over that of the starved rats cannot be due to the activating effects of such contractions.

The second physiological mechanism is the thermoregulatory relationship between food intake and activity. Brobeck, Wheatland and Strominger (1947) proposed that running increases during starvation in order to maintain normal body temperature. Since sufficient food is not being consumed to produce heat and food deprivation results in the loss of insulating fat stores, increased heat production is attained by increased activity levels. Evidence for a thermoregulatory mechanism was suggested by Stevenson and Rixon (1957). These authors found an inverse relation between environmental temperature and activity levels in rats. In addition, Stevenson and Rixon (1957) found that body temperature of rats falls during starvation when activity is restricted but not when allowed. Stevenson and Rixon (1957) concluded that "increased activity during starvation is related to the maintenance of body temperature and is interrelated with food intake in this function" (p. 582).

Several studies have produced results which contradict the thermoregulation hypothesis (e.g., Campbell, 1964; Campbell and Lynch, 1967, 1968). For example, Campbell (1964) found that a decrease in body temperature (due to environmental temperature changes) is not sufficient to produce activity level increases (measured in stabilimeter cages) by water and food deprived rats. Interestingly, Campbell (1964) also produced data which argues in favor of a thermoregulation hypothesis. He found that wheel running activity declined with increases in environmental temperature. Further, he found that food deprived rats survived longer than free-feeding rats when subjected to a high environmental temperature (95 degrees Farenheit) when both groups were given running wheel access. Free-feeding rats continued to eat despite the high temperature and died due to heat exhaustion whereas food deprived rats did not. Rectal temperatures were lower in the food deprived rats than in the free-feeding rats suggesting that food intake increased metabolic rate and body temperature. Similarly, free-feeding rats housed in stabilimeter cages at 95 degrees Farenheit survived longer than free-feeding rats in running wheels at the same temperature. These studies support the hypothesis of Brobeck, Wheatland and Strominger (1947) that running by free-feeding or food deprived rats results in an increase in body temperature. However, Campbell's (1964) finding that a decrease in body temperature is not sufficient to produce activity level increases suggests that thermoregulation is not dependent on activity levels alone. This finding contradicts Brobeck, Wheatland and Strominger's (1947) attribution of increased running during food deprivation to thermoregulation.

Another literature indirectly supports a thermoregulatory relationship between eating and activity. This research investigates genetic obesity in rodents. In general, obese rats and mice demonstrate hyperphagia and a decreased capacity for fat thermogenesis. That is, these animals do not readily metabolize fat stores into available energy (cf., Bray and York, 1971; Tulp, 1984). Also, the majority of genetically obese rodents store an increased fraction of their food intake as fat compared to lean controls (Bray and York, 1971). Defective fat thermogenesis, particularly in brown adipose tissue, contributes to increased metabolic efficiency or fat storage when combined with increased food intake (Himms-Hagen, 1985). A notable exception is a study by Lee, Wang and Russell (1987) in which no difference in thermogenic response to cold stimulation or norepinephrine (which stimulates non-shivering thermogenesis) in LA/N-cp and lean control rats was found. Lee, Wang and Russell (1987) concluded that the development of obesity in the LA/N-cp rat cannot be due to a thermogenic defect in the brown adipose tissue as proposed by Tulp (1984).

Many studies examining genetically obese rodents note that hypoactivity characterizes these animals compared to lean controls (e.g., Bray and York, 1971; Mayer, 1953; Yen and Acton, 1972). These studies suggest that caloric expenditure via activity is decreased in obese rodents compared to lean controls. Corpulent rodents typically exhibit hypoactivity together with hyperphagia, increased metabolic efficiency, and impaired fat thermogenesis. Also, these rodents do not increase activity to maintain body temperature and cannot utilize fat stores to do so. Thus, obese rodents may be hyperphagic to maintain insulative fat stores.

In conclusion, two physiological mechanisms which have been proposed to mediate the relationship between running and eating were discussed. Richter (1927) found a correlation between stomach contractions and activity and proposed that the contractions produced the increase in observed activity. Another mechanism, thermogenesis, suggests that an increase in activity during food deprivation results in an increase in body temperature. There is experimental evidence for (e.g., Stevenson and Rixon, 1957) and against (e.g., Campbell, 1964) this hypothesis. In addition, the study of genetic obesity in rodents shows that obese rodents have impaired fat thermogenesis, hypoactivity and hyperphagia (cf., Tulp, 1984; Yen and Acton, 1972). As these corpulent rodents do not increase activity to offset impaired fat thermogenesis, they become hyperphagic and increase insulative fat stores instead. Taken together, these studies suggest that thermogenesis (if not impaired as in genetic obesity) through increases in activity and/or utilization of fat stores may be used to maintain body temperature in rats that are food deprived and have increased activity to high levels in activity-anorexia.

2. Endogenous opioid peptides and activity

In the physiological literature, the endogenous opioid peptides have been divided into three main families based on criteria such as cellular localization, tissue of origin, pathways of distribution, receptor sites and precursors. These families are beta-endorphins, dynorphins and enkephalins (Goldstein, 1984; Herz and Millan, 1984). In some studies, the term "endorphin" is used to describe all endogenous opioid peptides that activate opiate receptors (Cox and Baizman, 1982; Hiller, 1982), and in other studies endorphin refers to beta-endorphins only (e.g., Amir, 1982). For the sake of simplicity, the term endorphin will refer only to beta-endorphin.

Epling and Pierce (1988) hypothesized that one or more types of endogenous opioids are activated by the excessive activity observed in activity-anorexia. Studies by Amir (1982), Appenzeller, Standefer, Appenzeller and Atkinson (1980), Lord, Waterfield, Hughes and Kosterlitz (1977) and Walker, Berntson, Paulucci and Champney (1981) suggest that the particular type of opioid involved in excessive activity is endorphin. In this regard, Lord, Waterfield, Hughes and Kosterlitz (1977) found that endorphin binds to its own receptor sites and those of other opioids equally well. These authors speculated that endorphin may interact with all opiate receptor sites as it is the precursor of other opioid peptides. ~~In addition~~, Amir (1982) found that endorphin is released from the pituitary gland and brain in response to physical stressors such as forced swimming. Forced swimming resulted in an immobility response by rats similar to that elicited by small injections of endorphin (Bloom, Segal, Ling and Guillemin, 1976). Pretreatment with naloxone resulted in dose-dependent decreases in endorphin-induced immobility produced by forced swimming (Amir, 1982). Walker, Berntson, Paulucci and Champney (1981) using naloxone also found a decrease in activity following endogenous opioid release by a 30min forced swim in rats. Appenzeller, Standefer, Appenzeller and Atkinson (1980) found that endorphin levels in humans are significantly increased following a marathon compared to pre-race levels. Farrell (1985) also found that blood plasma levels of endorphin were elevated in humans after exercise. Finally, Walker, Berntson, Paulucci and Champney (1981) cite several studies which show that naloxone does not reverse some effects produced by enkephalin release. Taken together, these studies suggest that endorphin is involved in high rate running.

Other studies have found endogenous opioid involvement in non-excessive activity in rats (e.g., File, 1980; Walker, Berntson, Paulucci and Champney, 1981). For example, File (1980) found that naloxone (1, 2 and 4mg/kg) resulted in dose-dependent decreases in exploratory behavior by rats. Also, social interaction and motor activity by pairs of rats was reduced by naloxone (2mg/kg). Walker, Berntson, Paulucci and Champney (1981) found that baseline activity levels of rats was reduced 50% by naloxone (2mg/kg). These studies, together with studies reviewed above (e.g., Appenzeller, Standefer, Appenzeller and Atkinson, 1980), suggest that endogenous opioids, endorphin in particular, are released during forced, voluntary or low rate physical activity.

Further support for Epling and Pierce's (1988) opioid hypothesis is found in studies examining the effects of the opiate antagonists naloxone and naltrexone on morphine-elicted changes in the activity of hamsters, rats and mice (e.g., Henry, Walker and Margules, 1985; Schnur, 1985; Schnur and Hang, 1987; Schnur and Raigoza, 1986; Vasko and Domino, 1978). For example, Schnur (1985) found that morphine (an opiate agonist) injections of 0.5 to 40mg/kg produced a brief initial dose-dependent decrease in activity followed by a dose-dependent increase in activity in hamsters. They also report that naloxone (0.4mg/kg) or naltrexone (1.0mg/kg) blocked these effects. Similar antagonization of morphine-elicited sedation and hyperactivity by naloxone (1.0mg/kg) was found by Vasko and Domino (1978) in rats. Finally, Henry, Walker and Margules (1985) report that morphine-elicited hyperactivity was blocked by naltrexone in mice. These studies show that the opiate agonist morphine produces increases in activity levels which can be blocked (and decreased) by opiate antagonists.

In conclusion, endogenous opioids particularly endorphin, are released during periods of activity (e.g., Amir, 1982; Appenzeller, Standefer, Appenzeller and Atkinson, 1980). Activity levels are decreased by the opiate antagonists naloxone and naltrexone, whether the activity is low (Walker, Berntson, Paulucci and Champney, 1981), exploratory (File, 1980), morphine-elicited (Schnur and Hang, 1987) or due to forced swimming (Amir, 1982).

3. Endogenous opioid peptides and feeding

In general, opiate antagonists such as naloxone and naltrexone reduce water and food intake in rats, humans, and tigers if the endogenous opioid system has been activated by food or water deprivation (e.g., Billington, Morley, Levine, Wright and Seal, 1985; Brands, Thornhill, Hirst and Gowdey, 1979; Brown and Holtzman, 1979; McLaughlin and Baile, 1984a, 1984b; Reid, 1985). For example, Brown and Holtzman (1979) found that naloxone (0.1 to 10mg/kg) reduced water or food intake following periods of water or food deprivation of 12 to 48h. In addition, naloxone reduced food intake in non-deprived humans (Cohen, Cohen, Pickar and Murphy, 1985) suggesting that the endogenous opioid system modulates non-deprived eating behavior as well. Finally, Sanger and McCarthy (1980) showed that morphine increased food and water intake by non-deprived rats - an opposite effect to that of naloxone on free-feeding food and water intake. These studies show that endogenous opioids are involved in deprived and non-deprived feeding.

However, activation of the endogenous opioid system by physical activity may have different effects upon feeding. For example, Davis, Lamb, Lowy, Yim and Malven (1985) found that rats which were forced to swim and which were injected with 2-deoxy-D-glucose (an endogenous opioid stimulus which inhibits glucose utilization resulting in increased feeding, cf., Thompson and Campbell, 1977) showed depressed post-exercise feeding. Other research has shown that opiate antagonists cause a reversal in morphine elicited behavior (e.g., Schnur and Hang, 1987). In general, morphine produces an increase in food intake (cf., Reid, 1985). However, Sanger and McCarthy (1980) found that morphine decreased food and water intake by 24h food deprived rats in a dose-related manner. Taken together, these studies suggest that excessive activity activates endogenous opioids which reduce eating when animals are food deprived.

Finally, studies which examined the treatment of human anorectics with opiate blockade by naloxone (Mills and Medlicott, 1984) and naltrexone (Luby, Marrazzi and Kinzie, 1987) provide additional evidence for opioid mediation of activity and eating. For example, Mills and Medlicott (1984) found that prolonged naloxone infusions (up to 61 days at 1.6 to 6.4mg/day) resulted in weight gain by anorectics. In addition, Luby et al. (1987) found that naltrexone treatment increased food intake resulting in substantial weight gain and decreased hyperactivity in their anorexic patients. These findings provide strong evidence for Epling and Pierce's (1988) hypothesis that "excessive physical activity activates one or more endogenous opioids that reduce appetite" (p. 480). Importantly, when endogenous opioids were blocked in these studies, high activity levels decreased and food intake increased.

In summary, endogenous opioids are involved in deprived and non-deprived feeding. However, endogenous opioids activated by excessive activity act to decrease feeding during food deprivation. In support of Epling and Pierce's (1988) opioid hypothesis, treatment of human anorectics by opiate antagonists found that opioid blockade decreased activity and increased feeding.

4. Endogenous opioid peptides and the hypothalamic-pituitary-gonadal axis

Although an exhaustive examination of the relationship between the endogenous opioid system and the hypothalamic-pituitary-gonadal (HPG) axis is beyond the scope of the present review, there are certain links between the HPG axis and the opioid system which implicate opioid mediation in human activity-anorexia (cf., Epling and Pierce, 1988). Many studies have shown that female anorectics and athletes have menstrual problems (e.g., Litt and Glader, 1986). For most anorectics, amenorrhea (cessation of menses) begins when body weight drops below the normal range (Casper, 1986; Warren, 1983) whereas the high physical activity observed in female athletes acts to potentiate amenorrhea prior to significant weight loss (Litt and Glader, 1986). However, in both female anorectics and athletes, amenorrhea often occurs before significant weight loss and is associated with poor nutrition (Litt and Glader, 1986; Warren, 1983).

Endocrine changes associated with excessive exercise and poor nutrition include lowered secretion of pulsatile luteinizing hormone (LH) from the anterior pituitary (Cumming, Vickovic, Wall and Fluker, 1985; Warren, 1983). Endogenous opioid involvement in the reduction of LH levels has been found by several researchers (e.g., Risch, Janowsky, Judd, Gillin and McClure, 1983; Ropert, Quigley and Yen, 1981). Elevated endorphin levels act to inhibit LH releasing hormone (LH-RH) from the hypothalamus (Risch, Janowsky, Judd, Gillin and McClure, 1983). As mentioned earlier, elevated endorphin levels are found in humans following exercise (e.g., Appenzeller, Standefer, Appenzeller and Atkinson, 1980). In addition, endorphin levels are increased in anorectics (Kaye, Pickar, Naber and Ebert, 1982). Interestingly, Ropert, Quigley and Yen (1981) showed that naloxone infusion (1.6mg/hour for

6h) significantly increased LH pulses over saline controls. Similarly, the suppressing effect of morphine on LH-RH can be blocked using naloxone (Pang, Zimmerman and Sawyer, 1977). However, Giusti, Torre, Traverso, Cavagnaro, Attanasio and Giordano (1988) did not find that naloxone (6mg/2h) increased LH release in anorectics or amenorrheic patients. Importantly, LH levels had already been increased by intravenous pulsatile LH-RH therapy in their study. These authors presumed that naloxone administration would result in an increase in LH-RH by decreasing endogenous opioid levels. However, as LH-RH therapy had already restored normal menses, no further increase in LH levels was required for normal functioning.

In summary, the above studies show that elevated endorphin levels inhibit LH-RH production resulting in menstrual dysfunction observed in anorexia nervosa. Further support for endorphin involvement in amenorrhea is gained as the use of naloxone results in increased LH levels critical for normal menses.

5. Summary

Recently, Epling and Pierce (1988) proposed that the endogenous opioid system mediates the relationship between activity and feeding in activity-anorexia. Studies have shown that the endogenous opioid system, particularly endorphin, is involved in the control of eating following exercise (e.g., Davis, Lamb, Lowy, Yim and Malven, 1985). In general, opiate antagonists (e.g., naloxone) decrease food or water intake if the endogenous opioid system has been activated by food or water deprivation (e.g., Brands, Thornhill, Hirst and Gowdey, 1979; Brown and Holtzman, 1979; McLaughlin and Baile, 1984a, 1984b; Reid, 1985). However, activation of the endogenous opioid system by physical activity may have different effects upon eating. For example, Davis, Lamb, Lowy, Yim and Malven (1985) found that rats which were forced to swim and which were injected with 2-deoxy-D-glucose showed depressed post-exercise feeding. Additional research showed that opiate antagonists cause a reversal in morphine elicited behavior (e.g., Schnur and Hang, 1987). In general, morphine produces increments in food intake (Reid, 1985). However, Sanger and McCarthy (1980) found that morphine decreased food and water intake in 24h food deprived rats. Overall, these studies suggest that excessive activity activates endogenous opioids which reduce eating when animals are food deprived.

Other studies have shown that exercise increases endogenous opioid levels in animals (e.g., Amir, 1982; Walker, Berntson, Paulucci and Champney, 1981) and humans (e.g., Appenzeller, Standefer, Appenzeller and Atkinson, 1980). As well, elevated endorphin levels are found in anorectics (Kaye, Pickar, Naber and Ebert, 1982). Endogenous opioids are activated by food deprivation (e.g., Brands, Thornhill, Hirst and Gowdey, 1979; Brown and Holtzman, 1979; Reid, 1985) and food deprivation increases activity (e.g., Cornish and Mrosovsky, 1965). Further support for an opioid hypothesis is gained by the research which has showed that elevated endorphin levels inhibit LH-RH production resulting in menstrual dysfunction observed in anorexia nervosa (Mills and Medlicott, 1984). In addition, naloxone administration results in increased LH levels critical for normal menses (Ropert, Quigley and Yen, 1981). Taken together, these studies suggest that endogenous opioids, particularly endorphin, may modulate the relationship between feeding and excessive activity in activity-anorexia.

D. Activity-Anorexia as an Animal Model of Psychopathology

Suomi (1982) defined animal models of psychopathology as "experimental attempts to reproduce the essential features of various human disorders in nonhuman subjects. Being models, they are basically empirical expressions of theories about human psychopathology ... (which reflect) ... a particular theoretical viewpoint" (p. 249). Animal models are developed primarily because of the ethical problems involved in doing controlled research with human subjects (Suomi, 1982). For example, withholding a drug which may alleviate cancer from certain "control" patients is not acceptable. However, before such a drug can or should be used with humans, rigorously controlled experiments can be done on animals to reduce eventual risk to human patients. Similarly, Suomi (1982) stated that animal models of psychopathology are "supposed to help investigators and practitioners better understand, diagnose, treat, and/or prevent the disorder being modeled" (p. 258). The criteria proposed by Harlow and Suomi (1974), McKinney and Bunney (1969), and Suomi (1982) are used to evaluate Epling and Pierce's (1988) "biobehavioral model of activity-based anorexia" as an animal model of certain types of human self-starvation or anorexias.

The criteria proposed by Suomi (1982) are divided into three main categories: "those dealing with the _validity_ of the animal model being evaluated, those dealing with the specificity or clarity of the model, and those dealing with its practicality" (p. 258). These criteria will be used in an evaluation of Epling and Pierce's model of activity-anorexia.

1. Validity

To assess the validity of Epling and Pierce's model it is necessary to determine in what ways activity-anorexia reflects central features of human anorexias. Importantly, the activity-anorexia model does not attempt to mirror all of the essential features of anorexia nervosa as listed in the DSM III-R (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition - revised, 1987) which are "refusal to maintain body weight over a minimal normal weight for age and height; intense fear of gaining weight or becoming fat, even though underweight; a distorted body image; and amenorrhea (in females)" (p. 65). Rather, Epling and Pierce focus on biobehavioral interrelations between food intake and exercise and have proposed activity-anorexia as a classification of certain instances of anorexia nervosa. Epling and Pierce clearly state that their "model does not, and cannot depict the complex (psychological or) sociocultural conditions that predispose some individuals to contact the basic process (of activity-anorexia)" (p. 482). In this regard, Beumont (1984) noted that comparisons of behavior patterns and their consequences are useful and the validity of an animal model "does not depend on underlying assumptions as to similarity of motivation or other internal psychological variables between the animal subject and the human patient" (pp. 177-178). Thus, Epling and Pierce's biobehavioral model does not have to account for predisposing psychological or sociocultural factors or presumably unique human symptoms such as body image disturbances (DSM III-R, 1987) to be a valid animal model.

The primary focus of activity-based anorexia may be best understood in terms of Epling and Pierce's summary of the biobehavioral processes involved: "Strenuous exercise reduces the value of food reinforcement and results in decreased food intake. Reduction of food intake increases the motivational value of physical exercise. This produces an escalation in activity that further suppresses appetite. Cultural practices of diet and exercise initiate this anorexic cycle, and once started the process is resistant to change ... Proximate physiological mechanism(s) appear to involve the endogenous opiate system that mediates the relationship between running and eating" (p. 475).

McKinney and Bunney's (1969) validity criteria state that in order to be a valid model, first, the symptoms suggested as key to a diagnosis of activity-anorexia should be present in both animal and human "activity-anorectics", and second, direct causes of the disorder in humans should also cause the parallel disorder in the animal species used. From the above summary, an increased level of physical activity resulting in decreased food intake initiates the activity-anorexia cycle. Importantly, an increased level of physical activity has been observed in significant proportions of anorectics by many clinicians (e.g., King, 1963). Some clinicians have viewed such increased activity as the anorectic attempting to enhance weight loss by exercising to increase caloric expenditure (e.g., Bruch, 1966) or as a form of denial (in the psychodynamic sense) of the emaciating effects of not eating (Seaver and

Binder, 1972). More recently, however, hyperactivity has been reexamined and "promoted" from a secondary symptom (e.g., Feighner, Robins, Guze, Woodruff, Winokur and Munoz, 1972) to a fundamental clinical sign in anorexia (e.g., Kron, Katz, Gorzynski and Weiner, 1978). For example, Kron et al. (1978) found that 25 of the 33 anorectics examined in their study, were "'hyperactive' immediately prior, or during, hospitalization, i.e., during the acute excessive-dieting and severe weight-loss phase ... (and) twenty-one of (these) 25 patients were also described as having been extremely active well before they had ever dieted or lost weight" (p. 435). These authors concluded that "the hyperactivity of anorexia nervosa is one of the earliest signs to appear in the illness and one of the last to subside" (p. 437). Similarly, Katz (1986) described two male anorectics for whom involvement in excessive running was a precursor in the development of anorexia nervosa. Taken together, these studies support Epling and Pierce's review of animal research which shows that excessive activity preceeds and precipitates lowered food intake in activity-anorexia.

Case studies by Katz (1986) and Kron et al. (1976) also support Epling and Pierce's "second symptom" of the activity-anorexia cycle. That is, reduction of food intake (caused by the initial increase in exercise) promotes an increase in activity which further suppresses eating. This effect is found in animal studies examining self-starvation in rats (e.g., Routtenberg and Kuznesof, 1967) and other rodents (e.g., Cornish and Mrosovsky, 1965). In humans, Kron et al. (1976) found that "starvation may further impose an abnormal and poorly organized pattern of increased motor behavior (during the acute phase of anorexia nervosa) onto a basic hyperactivity that antecedes the acute phase of the illness" (p. 437). These authors noted that it was during this phase of the illness that the patients were rapidly losing weight and engaging in "excessive and bizarre dieting" (p. 439). Similarly, Katz (1986) noted that his patients began engaging in unusual eating habits after activity had reached excessive levels. For example, one patient had increased his running level to approximately 50 miles/week while eating only salads, coffee or diet soda, and eventually bingeing on a regular basis (p. 75). Katz' (1986) second patient had increased his weekly running to 90-100 miles during a period of caloric reduction and concommittantly stopped eating meat. This patient subsequently became depressed (after a knee injury) and began bingeing, gorging, and vomiting while maintaining his running level. In both the Katz (1986) and Kron et al. (1976) studies it is clear that food reduction further increased activity levels which lead to greater suppression of eating.

To summarize thus far, two "symptoms" specified by Epling and Pierce as central to activity-anorexia are seen in certain cases of human anorexia. First, increased activity results in decreased food intake, then, the reduction in food intake results in a further increase in activity and further suppression of eating. As mentioned above, Epling and Pierce do not attempt to describe commonalities in terms of predisposing factors between animals and humans, but focus instead on the interrelationship of food intake and activity which consistently results in the self-starvation phenomenon in animals (e.g., Routtenberg and Kuznesof, 1967) and humans (e.g., Katz, 1986). Once predisposed to develop activity-anorexia, the direct causes involving the relationships between activity and food intake appear similar in all species.

The third validity criterion to be addressed is that of a similar underlying physiological mechanism involved in activity-anorexia in both animals and humans (Harlow and Suomi, 1974). Epling and Pierce propose that endogenous opioids may mediate the relationship between activity and food intake. The evidence of such endogenous opioid mediation is strongly supported by the physiological literature. Briefly, endogenous opioids are released during periods of excessive activity in rats (e.g., Amir, 1982) and humans (e.g., Farrell, 1985). Such activity levels are decreased by the opiate antagonists naloxone in rats (e.g., Walker, Berntson, Paulucci and Champney, 1981) and naltrexone in humans (e.g., Luby, Marrazzi and Kinzie, 1987). Naloxone or naltrexone also decreases food intake if the endogenous opioid system has been activated by food deprivation (e.g., Brown and Holtzman, 1979). However, the activation of the endogenous opioid system by physical activity may have different effects upon eating. For example, Davis, Lamb, Lowy, Yim and Malven (1985) found that rats which were forced to swim and then injected with 2-deoxy-D-glucose (an endogenous opioid stimulus which inhibits glucose utilization resulting in increased feeding) showed decreased post-exercise feeding. Other research has shown that opiate antagonists cause a reversal in morphine (an opioid agonist) elicited behavior (e.g., Schnur and Hang, 1987). In general, morphine produces an increase in food intake (cf., Reid, 1985). However, Sanger and McCarthy (1980) found that morphine decreased food and water intake in 24h food deprived rats. These studies suggest that excessive activity activates endogenous opioids which reduce eating when animals are food deprived. In summary, the research examining the endogenous opioid system and activity and the endogenous opioid system and feeding in humans and animals strongly supports Epling and Pierce's contention that endogenous opioids mediate the relationship between activity and food intake.

The final validity criterion to be addressed is that "procedures that reverse the disorder in humans should be therapeutic to the species in which the model has been produced" (Suomi, 1982, p. 258). As described above, opiate antagonist treatment has been shown to decrease endogenous opioid mediated activity levels in humans (e.g., Luby, Marrazzi and Kinzie, 1987) and animals (e.g., Walker, Berntson, Paulucci and Champney, 1981). In addition, Luby et al. (1987) found that human anorectics treated with naltrexone increased food intake and gained weight concommittant with decreased activity levels. Conversely, Sanger and McCarthy (1980) found that morphine decreased food intake in food deprived rats. In addition, Boer (unpublished data) found that naloxone adminstration decreased daily running levels of rats compared to saline running levels of the same rats (naloxone and saline were administered on alternate days). Taken together, these studies suggest that the administration of opiate antagonists is therapeutic to both human and animal activity-anorectics.

In summary, four validity criteria proposed by McKinney and Bunney (1969), Harlow and Suomi (1974), and Suomi (1982) were applied in an evaluation of activity-based anorexia as a model of human psychopathology. The evidence reviewed supports the validity of this model as "the more of these (validation) criteria a given animal model is able to satisfy, the more valid that model will be" (p. 258). In conclusion, Epling and Pierce's model appears valid, however, "our ability to determine the validity of any part of any animal model will only be as complete as our current knowledge of the human disorder being modeled" (Suomi, 1982, p. 259). Thus, as more clinicians come to see hyperactivity as a primary and not secondary symptom, and the interrelationship between activity and food as central features of anorexia in humans, Epling and Pierce's animal model will correspondingly increase in validity.

2. Specificity

Specificity or clarity criteria evaluate an animal model "in terms of what it can tell us about the human disorder" (Suomi, 1982). Such criteria have been outlined by Abramson and Seligman (1977): "(a) Is the experimental analysis of the laboratory phenomena thorough enough to describe the essential features of its causes as well as its prevention and cures? ... (b) Does the laboratory model describe in all instances a naturally occuring psychopathology or only a subgroup?" (p. 5). In addition, specificity criteria are concerned with how parsimonius the model is in accounting for the modeled disorder (Suomi, 1982). Suomi (1982) warns of dangers inherent in oversimplifying "in the name of parsimony: ... (by) taking too simplistic a view of such phenomena we may be inadvertently overlooking contributing factors that have crucial implications for diagnosis, treatment, or prevention" (p. 259).

As reviewed in the previous section, the experimental evidence for Epling and Pierce's model provides strong support for the essential causal factors delineated by the model and also for "cures" involving control of such factors (e.g., Luby et al., 1987). Also, Epling and Pierce do not attempt to explain all cases of anorexia nervosa through the use of their model, rather "activity-anorexia may be viewed as one type of self-starvation that may occur in humans" (1988, p. 482). By limiting the applicability of their model to certain instances of human anorexia in which exercise and food intake interrelate in a specific manner, Epling and Pierce have not oversimplified "in the name of parsimony" (Suomi, 1982).

Finally, for the sake of terminological clarity, Epling and Pierce's term "activity-based anorexia" appears to be more appropriate than previous usages of the term "anorexia" when used in conjunction with animals. In activity-based anorexia the "loss of appetite" or "anorexia" is consequent to increased activity. In other "animal anorexias", such as fasting during hibernation or incubation (cf., Mrosovsky and Sherry, 1980), the use of the term "anorexia" is silly as the animals simply stop eating and engage in different behaviors (e.g., sleeping). Loss of appetite is observed in terms of declining food intake with progressive weight loss and increasing activity in Epling and Pierce's model, whereas loss of appetite during hibernation or incubation is simply inferred from a cessation in eating when doing so would conflict with important phylogenic behaviors. To call hibernation an "anorexia" would be to commit a teleological fallacy in that the description of the behavior (not eating) determines an inferred causal process (loss of appetite).

3. Practicality

The last criterion is concerned with "the practicality of the animal model for diagnosing, understanding, and ultimately curing the corresponding human disorder" (Suomi, 1982, p. 260). For example, an animal model of psychopathology may be experimentally valid for the diagnosis of a specified disease (e.g., whole rat brain myelin assays for multiple sclerosis) but not practical (e.g., not many persons would want this definitive test). Thus, empirical validity does not necessarily imply practical usefulness. However, the interrelation of running and eating in activity-anorexia proposed by Epling and Pierce has been supported in terms of the specification of excessive levels of activity and consequent suppression of food intake being central to the diagnosis of certain human anorexias (e.g., Katz, 1986; Kron et al., 1978). Further empirical findings which have clinical support include endogenous opioid system involvement in the maintenance of the anorexic cycle as shown by studies using opiate antagonists to alleviate anorexic symptoms such as hyperactivity, low food intake and weight loss (e.g., Luby et al., 1987).

4. Conclusion

The criteria outlined by Suomi (1982) and others (e.g., Abramson and Seligman, 1977) provide guidelines to allow the evaluation of animal models of psychopathology. As described above, activity-based anorexia appears to satisfy many of these criteria. This may be due to the fact that this model does not attempt to replicate the entire symptomalogy of the human disorder anorexia nervosa. Rather, Epling and Pierce have built their model on extensive empirical findings which implicate a localized set of interrelated phenomena involving activity and food intake in the causation of activity-anorexia. These findings were then confirmed in certain cases of human anorexia (e.g., Katz, 1986) and "cures" proposed by the model were evaluated as successful (e.g., Luby et al., 1987). Thus, activity-anorexia appears to be "one instance of such a classification (of human self-starvation) that could account for many instances of 'anorexia nervosa'" (p. 475). Further research regarding the determination of excessive activity and suppression of food intake as causal symptoms in certain cases of human anorexias may possibly result in therapeutic interventions acting in a preventative manner earlier in the anorexic cycle than is typically encountered in the clinical literature (e.g., Katz, 1986).

Interestingly, Epling and Pierce's "biobehavioral model" is best supported in a therapeutic sense by "biobehavioral treatment". For example, opiate blockade resulting in decreased activity, increased food intake, and subsequent weight gain (Luby et al., 1987). Finally, the ultimate usefulness of this model depends on additional research which continues to draw parallels between the animal model and the human disorder modeled in terms of diagnostic and therapeutic efficacy. Such research would encourage clinical acceptance of the model and its implications for treatment.

Appendix Table 1

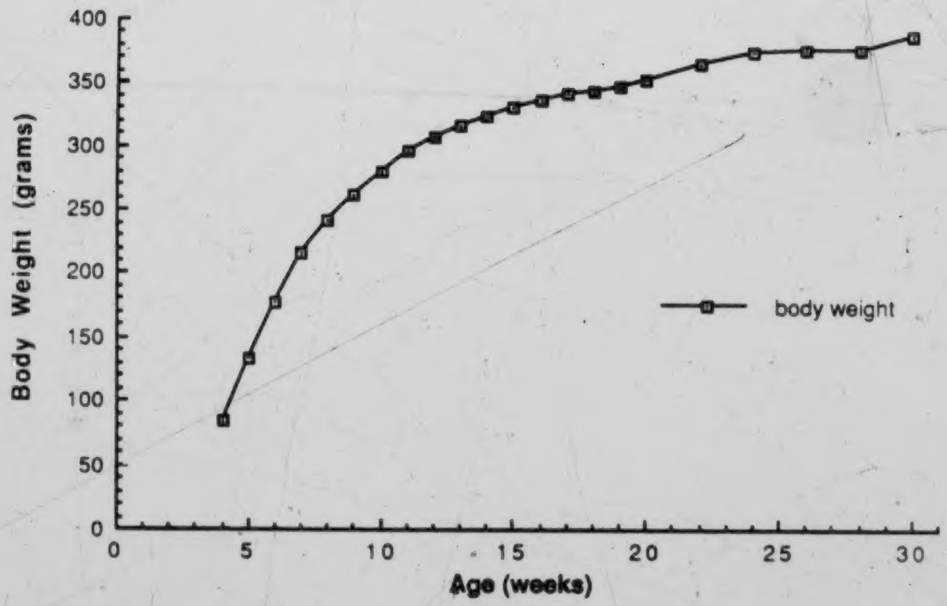
Average, standard deviation and range of daily
body weight for ad libitum food and water (controls)
JCR:LA/N-cp (lean) male rats (N=10) from 4 to 30 weeks

Age (weeks)	Body Weight (gms)	
	Average (S.D.)	Range
4	84.3 (14.5)	62-111
5	132.6 (17.0)	107-163
6	177.7 (15.9)	149-204
7	215.1 (15.8)	186-240
8	241.8 (14.4)	213-265
9	262.0 (15.7)	231-286
10	280.0 (16.1)	245-308
11	295.2 (15.4)	263-322
12	307.0 (15.3)	276-332
13	315.3 (14.9)	286-334
14	324.1 (16.9)	291-346
15	331.0 (17.7)	297-356
16	335.9 (17.5)	301-355
17	342.3 (19.2)	306-363
18	344.0 (20.0)	307-360
19	347.6 (19.3)	317-370
20	352.9 (19.1)	326-376
22	365.4 (17.0)	337-384
24	374.7 (13.6)	346-388
26	376.6 (14.0)	352-397
28	376.0 (15.6)	348-400
30	386.8 (14.7)	357-407

Appendix Table 2

Average and range of daily body weight and wheel turns for ad libitum running controls (N=5) for experiment one.

Days	Body Weight (gms)		Wheel Turns	
	Average	Range	Average	Range
1	188.2	180.3-195.3	688.4	474-815
2	184.8	178.5-189.7	940.2	521-1402
3	188.8	183.5-194.5	1280.6	1073-1713
4	194.5	189.3-199.4	1388.2	1004-2121
5	200.1	196.4-205.5	1875.8	1432-2887
6	205.4	199.9-209.2	2343.4	1405-3996
7	212.1	208.0-219.2	3035.8	2225-5003
8	217.0	210.5-224.4	3601.0	2396-6734
9	222.9	216.3-227.8	5266.4	2651-8176
10	228.1	218.1-236.7	4928.4	2043-9818
11	232.6	225.3-239.3	5102.4	1888-9967
12	237.1	227.9-245.1	7042.3	2220-10657
13	240.6	229.1-248.1	5921.2	2877-10838
14	242.5	229.5-251.1	5891.4	2949-9989
15	247.9	238.0-260.3	5297.2	2576-7438



Appendix figure 1: average body weight for ad libitum food and water JCR:LA/N-cp (lean) male rats (N=10) age 4-30 weeks.